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The American Heart Journal

VOL. 11 JANUARY, 1936 No. 1

Original Communications

THE COLD PRESSOR TEST FOR MEASURING THE REACTIBILITY OF THE BLOOD PRESSURE: DATA CONCERNING 571 NORMAL AND HYPERTENSIVE SUBJECTS*

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THE reactibility of the blood pressure is an index of vasomotor tonus. Studies by many workers have demonstrated that the systemic blood pressure is variable and reacts to many forms of stimulation.[1, 2, 3] A detailed study of this variability is time consuming and involves numerous estimations of blood pressure in short intervals of time. Many procedures have been tried by us and others; none has had certain or consistent pressor effects on the blood pressure. In 1932 we reported a simple procedure carried out by immersing the extremity in ice water. Measured cold, applied locally, produces a strong, thermosensory stimulus with vasopressor effects in 99 per cent of all subjects. Repetition of the test daily for a period of time shows a remarkable constancy in the response of the blood pressure. As far as known, the response of the blood pressure is characteristic for the individual and probably remains so throughout life. Confirmation of the specificity of the cold pressor test has been given by Briggs and Oerting,[4] who studied the reaction of 124 normal and hypertensive subjects. Dickman and Michel[5] have presented similar confirmation as a result of the study of the reaction of a group of pregnant and nonpregnant women.

TECHNIC OF THE COLD PRESSOR TEST

The subject is allowed to rest in a supine position in a quiet room for from twenty to sixty minutes. Several readings of the blood pressure are taken until a basal level has been approximated. The cuff of the sphygmomanometer is placed on one arm of the subject, and the opposite hand is placed in ice water (4° C.) to a point just above the wrist. Readings of the blood pressure are taken at the end of thirty seconds and

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again at the end of sixty seconds. The maximal reading obtained while the hand is in the ice water is taken as the index of the response. The hand is removed from the ice water, and readings are taken every two minutes until the blood pressure returns to its previous basal level. The maximal response usually occurs within thirty seconds. The blood pressure of subjects with normal levels of blood pressure returns to the basal level within two minutes. In the presence of established hypertension, there frequently is a delay in return of the blood pressure to the previous level. Subjects vary greatly in their sensitivity to ice water; for a few, the time of immersion is limited by the pain caused by the cold. There is no relationship between the degree of sensitivity and the response of the blood pressure. No untoward effects have occurred among hypertensive subjects, although increases in blood pressure to the capacity of the sphygmomanometer are occasionally noted.

Two values seem of significance in the cold pressor reaction: first, the increase in the blood pressure from basal to maximal points, which we have designated as the "response or range"; and second, the maximal values obtained in the systolic and diastolic pressures, which we have designated as the "ceiling" for the cold test stimulus. This ceiling is held for a variable time after application of the test. Which of these values is more useful is not known as yet. There is a certain error in the "range" as basal levels may be difficult to obtain.

MECHANISM OF THE REACTION

The most probable explanation of the cause of the rise of blood pressure in the cold pressor test is that the response is a widespread vasopressor reaction initiated through a neurogenic reflex arc. There is no significant change in cardiac rate or in cardiac output during the test. The speed of the reaction and the fact that the reaction is present in completely adrenalectomized dogs and in human beings who have Addison's disease are proof that epinephrine is not the primary factor in producing the reaction. The possibility of a local hormonal substance being generated in the immersed hand as a result of the direct action of the cold is unlikely, as the reaction is not inhibited by a tourniquet placed around the arm so as to shut off the circulation.

CONSTANCY OF THE REACTION

The test has been repeated one or more times after intervals of from three months to three years on twenty-five subjects whose blood pressures were normal and on twenty subjects who had essential hypertension. Four subjects whose blood pressures were normal were subjected to the test at the same time of day, three times a week for four weeks. Two subjects whose blood pressures were normal were subjected to the test twice a day for two weeks. One woman whose blood pressure was normal but who showed an abnormal range and abnormal maximal re-

sponse was subjected to the test fifty-six times in two years. There was an average variation in range of response of only 10 per cent in the group of patients who were subjected to repeated tests. In no case did a subject with a range of less than 18 mm. of mercury in systolic and diastolic pressures give a subsequent reaction in the abnormal range, and in no case did a subject who revealed an abnormal range give a normal reaction. Several subjects who gave reactions in the maximal range of normal on repeated tests gave occasional reactions in the minimal range of the abnormal. This type of subject we have placed in an indeterminate group. We have insufficient data to say what the possible effects of seasonal variations on this reaction are. Subjects with hypertension always give a reaction which is abnormal in maximal response, but repeated tests in months or years may show an increase in range and in maximal response, which correlates with increases in the clinical severity of the hypertension.

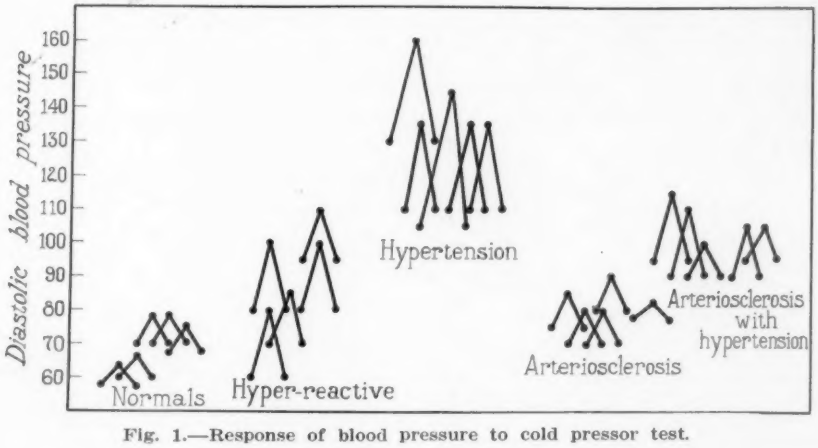

Fig. 1.—Response of blood pressure to cold pressor test.

THE EFFECT OF AGE ON THE REACTION

In the group in which there were normal levels of blood pressure and normal reactions, there was no significant change in the range of the reaction with increasing age (Table I). In the entire group with normal levels of blood pressure, there is a definite increase in the range of the reaction in the latter decades of life. This may be interpreted as indicating that an abnormal hypertonicity of the vasomotor system may increase in intensity with increasing years of life.

Data

We have made two previous preliminary reports on the results obtained with this test.[6] The present report is based on an observation extending over a period of three years and the application of the test to 571 subjects. The test has been repeated a varying number of times on a number

TABLE I

EFFECT OF AGE ON THE RESPONSE TO COLD PRESSOR TEST

AGE IN YEARS	NORMAL BLOOD PRESSURE AND NORMAL REACTIONS			NORMAL BLOOD PRESSURE (ENTIRE GROUP)		
	NUMBER	SYSTOLIC MM. OF MERCURY	DIASTOLIC MM. OF MERCURY	NUMBER	SYSTOLIC MM. OF MERCURY	DIASTOLIC MM. OF MERCURY
0 to 20	71	11.3 ± 0.84	9.4 ± 0.65	89	13.4 ± 0.91	12.3 ± 0.84
20 to 40	153	10.7 ± 0.93	9.5 ± 0.74	201	12.9 ± 0.87	11.8 ± 0.82
40 or more	64	11.6 ± 0.76	9.9 ± 0.68	98	19.6 ± 1.8	18.4 ± 1.6

of subjects. The entire group can be divided into three categories (Fig. 1). Group 1 includes subjects with normal levels of blood pressure and minimal or normal reactions of the blood pressure to the cold test. These individuals are designated as "normal reactors." They include normal persons and subjects suffering from a variety of diseases not associated with hypertension. Group 2 includes subjects with normal levels of blood pressure who react excessively to the cold test. These individuals we have designated "normal hyperreactors." Group 3 includes subjects with increased levels of blood pressure and other evidences of essential hypertension. A summary of the data in the three groups is shown in Table II.

TABLE II

SUMMARY OF DATA IN COLD TEST

SUBJECTS			MEAN RISE IN BLOOD PRESSURE	
	NUMBER	AGE, YEARS	SYSTOLIC MM. OF MERCURY	DIASTOLIC MM. OF MERCURY
Normal blood pressure	288	4 to 86	11.4 ± 0.9	10.6 ± 0.9
Hyporeactors (0 to 22 mm. of mercury)				
Hyperreactors (22+ mm. of mercury)	90	4 to 75	29.4 ± 4.2	24.5 ± 2.6
Hypertension				
Organic	127	24 to 64	47.2 ± 10.5	34.3 ± 7.9
Preorganic	66	25 to 62	34.4 ± 7.7	25.4 ± 4.5

Group 1, Normal Subjects.—In this group are those subjects with normal blood pressure and with minimal increase in blood pressure. The mean increase in this group was 11.4 mm. of mercury for the systolic and 10.6 mm. of mercury for the diastolic pressure. The values were from 0 to 22 mm. of mercury. The latter was tentatively placed as the upper limit of the normal response. In 96 per cent of those cases in which there was a normal or minimal response, the rise in systolic and diastolic blood pressure was less than 15 mm. of mercury.

Group 2, Normal Hyperreactors.—This group comprises ninety subjects of both sexes. Many normal hyperreactors were found in the course of general examination at the clinic. The readings of the blood pressure,

when taken under usual conditions, always were in the range of the normal. The ages of these subjects varied from four to seventy-five years. The value for the mean rise in blood pressure with the cold pressor test was 29.4 mm. of mercury for the systolic and 24.5 mm. of mercury for the diastolic pressure. This group is of great significance, and the crucial question is, do these subjects represent potential hypertension? Complete proof of this assumption is not at hand, but there is some evidence that such is the case. A careful investigation of the family history of these subjects, as related to possible incidence of hypertension, discloses that of these ninety subjects who revealed a hyperreaction, seventy-eight had a positive family history of hypertensive cardiovascular disease. If this is compared to the family history of hypertensive cardiovascular disease among 14 per cent of the group of subjects with normal reactions, the significance of the hyperreaction in "normal subjects" becomes more impressive. There is some additional proof accumulating. Of the original group of eight "hyperreactor normals" reported in 1932, three have developed clinical degrees of essential hypertension with elevation of the blood pressure and demonstrable hypertensive changes in the retinal arterioles. Brief protocols of the three cases are as follows:

CASE 1.—A woman was admitted to the clinic seven times in all. Previous to the time the cold pressor test was devised, her relevant history was as follows: On her examination in 1925 she was thirty years old and had bronchiectasis. Her blood pressures, in millimeters of mercury, were 138 systolic and 74 diastolic. On a second admission in 1926, she had exophthalmic goiter, and a thyroidectomy was performed; her blood pressures, systolic and diastolic, taken at different times, were 126 and 80, 116 and 74, and 134 and 74. She was admitted the third time in 1928; the systolic pressure ranged from 124 to 132 and the diastolic from 82 to 84. In 1930, the blood pressures were 118 systolic and 80 diastolic. The fifth registration was in 1932, when the systolic pressure ranged from 116 to 120 and the diastolic from 65 to 75. With the cold pressor test, the blood pressures were increased from a basal level of 125 for the systolic and 80 for the diastolic to 165 for the systolic and 115 for the diastolic. Examination of the ocular fundi did not reveal anything abnormal. Inquiry concerning her family revealed that her mother, aged sixty-three years, had high blood pressure and that her father, aged sixty-five years, had high blood pressure and recently had had a coronary occlusion. A diagnosis was made of a prehypertensive state. On her sixth registration at the clinic, in October, 1933, daily readings of the blood pressure varied from 100 to 132 systolic and from 58 to 88 diastolic. The response to the cold pressor test was from a basal level of 120 for the systolic pressure and 75 for the diastolic to 165 for the systolic pressure and 110 for the diastolic. Examination of the ocular fundi revealed very slight narrowing of the retinal arterioles. The basal metabolic rate was −4 per cent. On her seventh visit to the clinic, in January, 1935, daily readings of blood pressure revealed a variation of from 150 to 155 systolic and from 100 to 105 diastolic. The response to the cold pressor test was from a basal level of 130 for the systolic pressure and 80 for the diastolic to a maximum of 175 for the systolic pressure and 120 for the diastolic. Examination of the ocular fundi disclosed narrowing of the retinal arteries, grade 2. The basal metabolic rate was −3 per cent. The diagnosis was essential hypertension in the preorganic stage.

CASE 2.—A man was forty-two years old on his first registration at the clinic in March, 1931. Many daily readings revealed a variation of from 126 to 140 mm. of mercury for the systolic and from 50 to 90 for the diastolic. Examination of the ocular fundi did not reveal anything abnormal. The response to the cold pressor test was from a basal level of 120 for the systolic pressure and 55 for the diastolic to a maximum of 150 for the systolic pressure and 100 for the diastolic. The diagnosis was thromboangiitis obliterans and a prehypertensive state. On his second visit to the clinic, in January, 1934, many daily readings of the blood pressure revealed a variation of from 108 to 140 systolic and from 65 to 85 diastolic. Examination of the ocular fundi disclosed some narrowing of the retinal arterioles. The diagnosis was the same as it had been at his previous visit to the clinic. On his third registration in January, 1935, the readings for the blood pressure, which were taken in the office, were 184 systolic and 110 diastolic, and 158 systolic and 95 diastolic. Hourly readings of the blood pressure, while the patient was resting, revealed a variation of from 140 to 165 for the systolic pressure and a variation of from 90 to 105 for the diastolic. The response of the blood pressure to the cold pressor test was from a basal level of 130 for the systolic and 80 for the diastolic to a maximum of 175 for the systolic and 110 for the diastolic. Examination of the ocular fundi revealed narrowing of the retinal arteries, grade 2, and sclerosis of the hypertensive type, grade 1. The diagnosis was thromboangiitis obliterans and essential hypertension.

CASE 3.—A woman was admitted to the clinic nine times in all. Previous to the time the cold pressor test was devised, her relevant history was as follows: On her first admission, in 1921, she was twenty-nine years old and her blood pressures in millimeters of mercury were 124 systolic and 76 diastolic. On her second admission, in 1927, she had acute catarrhal cholangeitis. Her blood pressures were 120 systolic and 72 diastolic. She was admitted again in 1928, 1929, and 1930. Her blood pressures during these visits ranged from 126 to 135 systolic and from 70 to 85 diastolic. On her sixth visit, in January, 1932, the blood pressure was 124 systolic and 74 diastolic. The cold pressor test revealed an increase in the blood pressure from a basal level of 110 systolic and 80 diastolic to a maximum of 150 systolic and 110 diastolic. Aside from this, examination did not reveal any abnormality. The diagnosis was a prehypertensive state. On her seventh visit, in July, 1932, seven daily readings disclosed a variation in systolic blood pressure of from 114 to 146 and a variation in the diastolic pressure of from 72 to 86. The basal metabolic rate was –12 per cent. On her eighth visit to the clinic, in July, 1933, the blood pressures were 135 systolic and 88 diastolic. On her ninth visit, in July, 1934, six daily readings disclosed a variation in the systolic blood pressure of from 140 to 175 and a variation in the diastolic pressure from 94 to 105. With the cold pressor test the blood pressure increased from a basal level of 128 systolic and 75 diastolic to a maximum of 180 systolic and 110 diastolic. Examination of the ocular fundi revealed narrowing of the retinal arteries, grade 2. The basal metabolic rate was –6 per cent.

A subsequent report will be made of the later developments in this group of normal hyperreactors. At present, we hold to the belief that these subjects have a constitutional abnormality and that essential hypertension eventually will develop in many cases.

Group 3, Essential Hypertension.—In this group were 193 subjects with essential hypertension. The ages varied from twenty-four to sixty-four years. This group was further divided into two groups, the organic type and preorganic type of hypertension. This division was based on

the evidence of the presence or absence of changes in retinal arterioles. The value for the mean rise in the blood pressure in the organic group was 47.2 mm. of mercury for the systolic and 34.3 mm. for the diastolic. In the preorganic group, the mean rise was 34.4 mm. of mercury for the systolic pressure and 25.4 mm. for the diastolic pressure. The low and high values in the entire group were from 22 to 120 mm. of mercury for the systolic pressure and from 20 to 70 mm. for the diastolic pressure. There was some delay in the return of the blood pressure to the previous basal level in both groups. Ninety-seven per cent of the subjects in the organic group and all of the subjects in the preorganic group had abnormal reactions in range. All of the subjects in the organic and preorganic groups had abnormal ceiling values.

COMPARISON OF THE "RANGE" VALUE WITH THE "CEILING" VALUE

An analysis of the ceiling value shows that 98.4 per cent of the normal subjects, with normal range, had a ceiling of less than 145 mm. of mercury in the systolic pressure and that 99 per cent had a ceiling of less than 95 mm. of mercury in the diastolic pressure. Seventy-two per cent of the normal hyperreactors had a ceiling of more than 145 mm. of mercury in the systolic pressure and more than 95 mm. of mercury in the diastolic pressure. There is a definite correlation between the range of the reaction and the maximal rise or ceiling. If, however, the ceiling alone is taken as a criterion, a small group of subjects who have very low basal levels and a high range will be overlooked. If the range alone is taken as a criterion, a small group of subjects for whom, for some reason, proper basal levels cannot be obtained, may be overlooked. Any standard point of differentiation between a normal and abnormal response or level of blood pressure must be arbitrary. From the data at hand, we can conclude that of the group of 388 subjects with normal levels of blood pressure, the ninety subjects with a definitely abnormal range presented presumptive evidence of a hyperreactive vasomotor tonus, as measured by the reaction of the blood pressure. The group of sixty-five subjects with abnormal ranges and with maximal reaction in systolic pressure to 145 mm. of mercury, or more, and in the diastolic blood pressure to 95 mm. of mercury, or more, gave definite evidence of an abnormal vasomotor tonus.

COMMENT

Several points seem to have been brought out definitely by this study. First, the response in blood pressure to a standard stimulation (cold) is fairly constant for the normal individual. Significant changes have not been demonstrated within a year or less. Second, a few "normal hyperreactors" have been observed sufficiently long for essential hypertension to have developed. Third, persistent abnormal pressor responses have not been demonstrated in disease states other than essential hypertension.

We submit the conception that essential hypertension affects only subjects who are hyperreactors. The corollary may not be necessarily true, that essential hypertension affects all hyperreactors. A group of healthy subjects in the later decades of life have been found who have hyperreactions and changes in the retinal arterioles which are indicative of essential hypertension, but who have normal or subnormal levels of blood pressure. A separate report will be made of this important group. A further question arises whether old age per se affects these responses. Our data indicate that normal reactions obtain in aged arteriosclerotic persons whose retinal arterioles do not show changes of hypertension. Subjects with hypertension and arteriosclerosis reveal hyperreactions. This information, while as yet not conclusive, seems to rule out a secondary form of hypertension as a result of the arteriosclerotic process, the so-called senile hypertension.

A demonstrable relationship is established between the ceiling and the response in blood pressure. If a subject has a maximal or ceiling level which exceeds 145 mm. of mercury for the systolic pressure and 95 mm. of mercury for the diastolic pressure, a hyperreactive response to the cold pressor test will be found in 97 per cent of the cases. A ceiling value of 100 mm. of mercury or more for the diastolic pressure shows a hyperreactive response in 100 per cent of cases.

The pressor responses in vasospastic disorders, Raynaud's disease, and neurocirculatory asthenia are inclined to fall in the upper range for normal subjects. In hyperthyroidism and neurocirculatory asthenia, there is an abnormal response in the systolic pressure only. This would lead one to surmise that acquired hyperreactions of nonhypertensive subjects do not attain values reached by the hypertensive subject and that this form of the hyperreactive state may vary with the course of the primary disease.

There seems to be a definite diagnostic value in the pressor reactions in separating the primary and the secondary forms of hypertension. The systolic forms of hypertension seen in neurocirculatory asthenia with tachycardia, in glomerular nephritis, and in hyperthyroidism give responses definitely less than do the preexistent and existent stages of essential hypertension, unless both conditions coexist. The question rises as to whether or not the excessive pressor reaction may be acquired. We have observed one case in which an acute hypertension developed in the course of encephalitis. As far as could be determined, there was no history of hypertension in the ancestry of the patient, but this information was not conclusive. Abnormal reactions have developed in the course of pregnancy, with a subsequent development of toxemia and a return to a normal response following delivery.[7] Further investigation is needed on this important point.

A conception is here presented that the abnormality of essential hypertension is an excessive response in the blood pressure to intrinsic and

extrinsic stimulation. This abnormality is an hereditary one, which appears early in life and remains during life. When the level of the blood pressure is elevated and clinical degrees of hypertension exist, the reactions then increase with increasing severity of the hypertension. This hyperreactive vasomotor mechanism may be an important factor in the production of arteriolar hypertrophy and in the subsequent development of the organic stages of the disease.

SUMMARY AND CONCLUSIONS

1. A simple, standard test to measure generalized vasomotor tonus has been devised in which ice water is used as a stimulus.

2. This test divides all subjects with *normal* blood pressure levels into two groups: those with "normal" or minimal reactions of blood pressure to the test, and those with "abnormal" or excessive reactions.

3. Ninety-eight per cent of all subjects with essential hypertension have abnormal ranges and abnormal maximal responses to the test.

4. Repetition of the test at intervals indicates that the reaction is a constant one.

5. There is a correlation between the range of the response and the maximal rise of the blood pressure.

6. The reaction probably is based on a generalized vascular constriction initiated through a neurogenic reflex arc.

7. A transition from the prehypertensive state to essential hypertension has been observed in three cases.

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PSYCHOANALYTIC OBSERVATIONS IN CARDIAC DISORDERS*†

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HARVEY'S discovery of the circulation of the blood and of the function of the heart as a pump was so revolutionary, so astounding, and so significant for the materialistic conception of human life that in many ways it may be said to have been the turning point in the career of modern medicine. Many pages have been written in extolling and elaborating its importance, an importance which perhaps cannot be overstated and for which all of us are glad to pay tribute to its modest author.

But in the enthusiasm over the great developments which followed this discovery, medicine lost sight of a nucleus of truth in the pre-Harvian conceptions, which died with his discovery. Because we learned that the heart was a pump we discarded the age-old notion that the heart was the seat of the emotions, and whereas the anatomical and physiological studies initiated by Harvey's discovery have made tremendous advances since his day, the intuitive linking of the heart with the emotional processes was allowed to wither under scientific neglect for over a century until revived by the experimental work of W. B. Cannon.

Such expressions as "heartsick," "hardhearted," "brokenhearted," "chickenhearted," etc., are remnants of the intuitive era of anatomical confusion. But their tribute to the popular overestimate of the heart as an organ expressing emotion is almost entirely ignored by medical science.

If we go back to Avicenna,[7] for example, we read such intuitive observations as the following: The author is describing the symptoms of love, a condition which he classified among mental diseases.

"In this way," he said, "it is possible, even though the patient may deny his feelings, to identify the person loved, and to base on this knowledge a mode of treatment. The method consists in repeating certain names while the patient's pulse is being read. As soon as the pulse shows any irregularity, the trial is stopped and one begins again. I have tried this method more than once, and discovered through its use the name of the person loved by the patient."

In recent times a few studies of the psychological factors in heart disorders have been written by cardiologists, almost none by psychiatrists. These usually refer with evasive generalities to the "impor-

*From The Menninger Clinic.
†Read at the Chicago Institute for Psychoanalysis, April, 1935.

tance'' of psychological factors therein, but unless observed in an individual who shows other and unmistakable neurotic stigmas, the details of the emotional disturbances are rarely linked definitely with the cardiac manifestations.

Numerous forward-looking internists have attempted to understand their patients with cardiovascular disease from the standpoint of psychopathology, but from the point of view of the psychoanalyst, they are limited in their approach by reason of the fact that only the conscious emotional factors are accessible to investigation by the technic ordinarily used. A few cardiologists[20, 14, 11, 19] point out that the treatment of certain cases of cardiac neurosis require technical psychotherapeutic methods in the hands of an expert; some of them suggest naïvely the occasional desirability of resorting to the aid of a ''neurologist.''[18, 2]

Extrasystole has been recognized as being produced by psychic stimuli (Kabakov,[12] Willius[27]), as is also the syndrome of paroxysmal tachycardia (Kure,[15] Willius[27]) and that of precordial pain.[16, 21, 1, 5] Although less frequently clearly psychological, auricular fibrillation and flutter have been regarded as ''functional arrhythmias in some cases'' (Friedlander and Levine[9]). Even acute dilatation of the heart has been reported[18] as ''caused by nothing else but dissociated fear in a patient with cardiac neurosis.'' The syndrome known as neurocirculatory asthenia (''soldier's heart'') is regarded by many cardiologists as neurosis (Kilgore,[14] Conner,[5] Willius,[27] White,[6, 8, 25, 26] Boas[3]).

From the point of view of the psychiatrist, the most gratifying study of the so-called ''cardiac neuroses'' by a cardiologist is that of Conner.[5] He distinguished between the psychoneurotic group in which there is fear but no heart symptoms and the neurotic group in which there are heart symptoms without conspicuous fear. He pointed out that in all these cases the psychogenic stimulus is more likely the chief etiological factor rather than an abnormally sensitive autonomic nervous system and that in these cases the stimulus is usually forgotten (in psychoanalytic parlance, repressed). He listed the common (superficial) psychogenic precipitating traumas as: (1) the thoughtless statement of some physician; (2) the knowledge of heart disease and/or sudden death in the family or friends; (3) the occurrence of some sudden symptom such as pain, which focuses attention on the heart; and (4) a profound emotional disturbance as in ''shell shock.'' He stated very definitely that treatment belongs essentially to the realm of psychotherapy.

The close interrelationship between organic heart disease and psychic stimuli are well recognized in angina pectoris, and well summarized in a recent paper by Katzenelbogen[13]: ''Clinical and anatomopathological observations brought to light the concept that the morbid manifestations of such organic disease *par excellence* as angina pectoris appear to be controlled by a functional factor. Such a belief

has its basis in the fact that one finds at post-mortem examination sclerosis of the coronary artery in persons who never had anginal attacks. Moreover, in certain patients who did suffer from typical attacks of angina pectoris and displayed evidence of marked excitability of the vegetative system, the anatomical examination did not reveal lesions in the myocardial vessels; nor could any lesion of the vegetative system be discovered."

PSYCHIATRIC STUDIES

Recently there have been a few reported studies of cardiovascular disorders from the psychiatric point of view. Wolfe[28] reported three cases of functional cardiovascular disease and reviewed briefly some previous psychiatric observations of these conditions. He noted the very frequent occurrence of intense repressed hatred, resentment, and strong guilt feelings in patients with increased tension and angina pectoris.

Braun[4] developed the thesis that the heart was the specific organ of anxiety, apparently failing to recognize the complex psychological features associated with anxiety. He devoted an entire chapter of his book to the diagnostic significance of the anxiety dream. MacWilliam[17] reported some physiological observations of the increase in blood pressure and heart action during sleep and in dreams. In Wolfe's study of the dreams in 100 cardiac patients he found the majority related to falling, to jumping, or to some life-threatening situation and that these occurred, in most cases, only at the time of an exacerbation of the cardiac illness.

Galli[10] has reported a series of psychiatric investigations of the "cardioneuroses" and "circulatory neuroses."

PSYCHOANALYTIC OBSERVATIONS

It is greatly to be regretted that some of the rich clinical material so elaborately studied from the physical and descriptive sides by the cardiologists could not similarly be subjected to penetrative psychiatric study. This lack of cooperation between cardiologists and psychiatrists is truly deplorable because it hinders both of them and retards scientific knowledge. The cardiologists acknowledge that they need psychiatric help in the understanding of their cases, and the psychiatrists would profit greatly to learn more of the ways in which thwarted instinctual demands are organically rather than behavioristically expressed.

Perhaps it is partly due to the fact that the psychiatrists have immolated themselves too much. They have talked about "schizophrenia" and "negativism" and "delusions" until the internists perhaps conclude that psychiatry has not advanced beyond the early days of preoccupation with the "insane" and is using an appropriate

vocabulary. The result is that many internists have rather scant conception of the advance which has been made in our ability to determine the precise qualify if not quantity of repressed emotion. Significant and valuable as are our advances in the knowledge of the heart as the result of the electrocardiograph, progress in psychological investigation has been even more advanced and revolutionary. Cardiologists who would deplore or be amused by the use of such vague terms as "heart trouble" or "heart stoppage" on the part of psychiatrists use equally naïve, vague, and unscientific designations for emotional states, and do so with complete obliviousness of how empty and unprecise they sound to one familiar with methods of careful emotional evaluation. To be sure, many psychiatrists are also guilty of using such vague and meaningless terms but this does not invalidate our thesis any more than does the fact that some cardiologists scoff at the electrocardiograph discredit its great value.

Of course the greatest single step in the more definitive recognition of specific emotional factors and vectors is the appreciation of Freud's concept of the unconscious. Intuitively every thoughtful person is aware of the existence of unconscious emotional forces in his thinking, acting and feeling, but there are strong repressive forces striving to deny it the consideration it deserves. Moreover, doctors in particular have been traditionally educated, unfortunately, to distrust their intuition.

The painstakingly extended field of psychoanalysis, however, has uncovered a mass of material which has given us a new orientation in the understanding of the emotions (just as Cannon's researches have enlightened us relative to the physiological machinery used in expressing these emotions). Freud discovered and taught us a technic for investigating the unconscious roots of conscious emotional and behavioristic expressions so that now in any particular case it is theoretically possible to be precise and explicit as to the deep psychological trends present, let us say, in a case of chronic endocarditis.

The practical difficulties in carrying through such an investigation are, unfortunately, very great. Clinical cooperation is rare, research funds are few, the expense in time and money is large. Hence it is only an exceptional case in which we have the opportunity to study the emotional life of the cardiac invalid beyond the superficial descriptive phase. Occasionally a cardiac patient comes under the scrutiny of psychoanalysis—perhaps for quite other than the cardiac symptoms. Under such circumstances a great deal is learned about the patient's emotional life, conscious and unconscious, and some of this naturally relates to the illness. In some instances it appears to relate so specifically to the illness that we may fairly say that the emotional factors perhaps enter into the etiology of the illness. This is not a

fact yet—it is not even a hypothesis. It is only a suggestion of a possibility which the clinical reports of observant cardiologists have already intimated as indicated above.

As yet, however, the material is much too limited for us to draw any conclusions. Very few psychoanalysts have reported the cases they have seen. This is partly due to the fact that they are so few in number and partly, upon the other hand, to the inconclusive nature of the findings. Psychoanalysts can study only a relatively small number of patients because each case requires such an enormous amount of time, and psychoanalysts who have spoken to the present writers about such cases usually add that it seems inconclusive and not particularly valuable to relate the details of one or two cases which they have studied in the light of the hundreds of thousands of cardiac cases which are being studied clinically.

The authors of this paper feel that we should not be deterred by these considerations from at least making a start in the recording of such observations. If it has no other effect, perhaps it will stimulate the development of some research in a cooperative way between the cardiologists and the psychoanalysts.

One of the cases reported in the psychoanalytic literature[22*] is the following:

A woman, thirty years of age, had a "heart neurosis" of several years' standing, evidenced by attacks of violent palpitation which lasted for hours and were accompanied by painful anxiety. Occasionally the pulse ceased, and it was necessary to revive her with camphor injections, black coffee and champagne.

Examination showed nothing beyond a slight irregularity and acceleration of the pulse. There was a scarcely perceptible struma parenchymatosa. Stekel suggested psychotherapy, to which she "was all the more ready to agree, having obtained no relief from all her water-cures, strophanthus, digitalis and caffein."

She began by saying that her early life had been uneventful, that she had married the man she loved when she was twenty-two years old and that he had been a model husband. She was sexually satisfied and was the mother of three children. The nervous condition began about four years after the marriage and was attributed to overwork, responsibility, worry and overexertion about household affairs. In the second interview she described the last and worst attack she had had.

This had occurred on the anniversary of her wedding day. Her husband's sister and her husband, Mr. X., had visited the patient and had quarreled violently, Mr. X. charging his wife with having a love affair with the family physician (the same one with whom the patient had become dissatisfied when she came to see Stekel). It developed that the patient had formerly been interested in this doctor and was terribly excited when it was suggested that this sister-in-law, of whom she had long been jealous, was the real object of the doctor's love. She fell down with a loud cry and was shaken with convulsions.

In later interviews the patient told of three similar attacks, all of which had taken place on her own and on friends' wedding days. She then admitted dissatisfaction with her marriage, saying that her husband was unfaithful, unkind, and

*It is only fair to say that Stekel, while regarded as intuitive, is not regarded by some as scientific in all of his work and is not a recognized psychoanalyst, i.e., in the sense of being a member of the International Psychoanalytic Association. This does not in our opinion disqualify the present observation.

did not appreciate her and that he suffered from ejaculatio praecox and often left her sexually unsatisfied. Finally she confessed that she had not really married her husband for love, but because she had been jilted by the man she loved and because she was greatly attracted to her future husband's sister, Mrs. X. All in all, her marriage had been a bitter disappointment.

In the further course of the analysis the patient recalled an incident of her childhood when she was six or seven years old. A lodger who lived with her family had showed her his erect penis, and she had been impressed with its immense size which she had exaggerated in her mind in the years that followed until she was greatly disappointed on her wedding night to find her husband's normally developed penis did not approach the gigantic size of the one in her imagination. She had wept for hours with palpitations and feelings of anxiety and had been entirely anaesthetic sexually.

When this childhood recollection came back to her the patient had an attack of palpitation, anxiety, and spasms and could not continue with the interview. The next day, however, she felt completely relieved and continued to improve until the attacks and palpitations entirely ceased. Six years later she was still well and happy, although she had had to face a severe psychic shock in a business bankruptcy. She had gone through two confinements easily and was contented in her marriage.

Stekel also cited the case of a man fifty-one years old.

A man of Herculean proportions who had never known a day's illness until one night he awoke with a feeling of being strangled. He fought for his breath, feeling that he was dying. The attack soon passed off, and he thought it was due to a heavy supper the evening before. A few nights later, however, he had another attack and from then on they occurred frequently in the day as well as at night. He consulted a physician friend who diagnosed his illness as incipient arteriosclerosis and told him that with care he might live two years longer. On the advice of his friend the patient entered a sanitarium. He became more and more dejected and felt that his death was approaching. Eventually he came to Stekel for treatment, in the course of which he discovered that the heart attacks originated in a severe psychic conflict. He had lost the woman he loved, and with whom he had had a liaison for five years, to his best friend. For many weeks prior to the onset of his symptoms he struggled with the thought that he must strangle his friend for this betrayal. The analytic treatment was successful, and the attacks entirely ceased. Ten years later the patient was still "perfectly well, happily married, and at the height of his creative powers."

In our own psychiatric practice we have seen many patients whose chief symptoms seemed to be referable to the heart. The presenting symptoms of precordial pain, dyspnea, palpitation, and tachycardia engage the patient's attention, and he in turn uses them to engage the physician's attention. They are his passport or ticket of admission to the land of illness with all its restrictions and its advantages. Some of the most alarming cases we have seen were in part the result of unfortunate suggestion on the part of well-meaning physicians who, themselves alarmed at some of the patient's symptoms, prophesied a serious outcome or showed so much solicitousness and anxiety over their discovery as to gratify to the fullest extent the patient's hopes and fears. The patient becomes enormously frightened but also very much gratified to find that at last he is able to make somebody come to his aid with a proper degree of concern. Many internists

have called attention to this mistake on the part of the examining physician (Shirley Smith, Conner, Reid, Willius, Kilgore). Occasionally we are able to find some conscious reason for the fear and for the excessive need for the protection afforded by the physician. Occasionally, also, organic factors are actually present and advanced to such a point where even the discovery and correction of the emotional factors is of secondary importance. For example, one patient who was able to escape from the necessities of married life with a husband whom she did not love but could not afford to leave developed a heart affliction (chronic mitral disease) which had apparently grown gradually over many years but which by the time we saw her was actually so far advanced as to be irreversible.

Others of our cases have been more accessible to penetrative psychological study. One, for example, was a man, sixty-one years of age, with a definite organic heart affection which seemed to us to bear a definite relation to his psychopathology.

CASE REPORTS

CASE 1.—A man, aged sixty-one years, had been subject for more than four years to attacks of severe chest pain which radiated down both arms to his wrists and was accompanied by diaphoresis. He had been to many doctors, all of whom agreed as to the seriousness of his illness and counselled rest. He began to have violent headaches. He was living very quietly; for a year and a half before consulting us he had given up work and followed a careful regime of breakfast in bed, staying in bed until noon, then dressing for lunch, resting several hours after lunch, going for a drive of a few miles in his car driven by a chauffeur, and then returning home to bed once more. In spite of all this he complained of never feeling or sleeping well.

Examination showed he had a generalized arteriosclerosis with symptoms indicating involvement of the cerebral and coronary arteries.

Coincident with or even antedating the onset of this patient's anginal seizures, he had begun to feel vaguely nervous, uneasy in the company of other people and troubled by dreams of the past (especially of old business associates) at night. For many years he had been troubled by severe constipation and a variety of other "colonic" complaints. By the time the patient came to us, his nervous complaints were preponderant and had attained the magnitude of an incipient paranoid psychosis. He confided in the doctor that he had masturbated and believed that all of the townspeople knew of his habit and were talking about him. He was also greatly troubled by erotic dreams in which an actual male bedfellow would usually become the object of his advances while he slept and often reprimand him for the advances.

The patient was a small-town wealthy business man, a bachelor in the presenium. His entire past history (including a predilection for prostitutes, a love for male company in hotels, and an absence of sustained interest in any woman) pointed to strong unconscious homosexual propensities, against which he had waged a successful struggle until recently. He had latterly shown a tendency to become excessively fond of young male employees in his home and although there had never been any history of overt homosexual practices, the approach of these inclinations to consciousness was undoubtedly responsible for some of the fear represented by the symptoms of the illness.

It is interesting that this individual showed a remarkable improvement in all of his symptoms as soon as he was admitted to the sanitarium (where, of course, he was protected against any such temptations). His paranoid trends resolved entirely. While there was considerable evidence of anatomical coronary artery disease, he exhibited a functional improvement in his cardiac status that was truly surprising. Whenever this patient contemplated returning to his home, his symptoms increased in severity. It was evident that, aside from the routine sanitarium therapy, the patient had derived considerable benefit from separation from the influences which had been stimulating his homosexuality excessively. He was able to make an acceptable transference to a doctor and thus relinquish much of his need for punishment and his paranoid and hypochondriacal defenses against homosexuality.

The fact of the patient's improvement was unquestionable, although it is difficult to assign to the psychological factors in his illness their exact proportions. It is, of course, entirely possible that the somatic and visceral disturbances incident to the presenium served as the initial traumata which broke down a well-sealed psychological system and then assumed definite rôles and were elaborated within that system.

In another case, the psychological investigation was carried much deeper.

CASE 2.—A male, aged forty years, was studied over a period of several years. He had persistent and distressing cardiac symptoms in the discussion of which he spent many hours. He complained of precordial and presternal pain with the radiation of the pains down the left arm to the fourth and fifth fingers. We do not believe he had ever read any textbook descriptions of angina pectoris, but there is considerable probability that he had known one or two men who had suffered from it, and his symptoms were strongly suggestive of it. He professed to be so distressed at being awakened in the night by these pains and the fear of death that he went to fully a dozen physicians over the country, most of whom told him they could not find anything organically wrong with his heart, and a few of them frightened him severely by looking grave, shaking their heads ominously, and telling him he was going to have to be careful. In order to eliminate the possibility of a mistaken diagnosis he was examined by several of our internists. An electrocardiogram and a roentgenogram of the heart were entirely normal. This was not, therefore, a case of organic heart disease, but only one in which the patient thought he had heart disease and professed that he suffered cardiac pain. Very early in the psychoanalytic conferences he commented on the fact that this pain seemed to develop at certain times when he felt guilty about sexual misadventures, and he spoke of the common knowledge that death sometimes follows intercourse. (This, of course, one cannot dispute. The fact is also referred to by many. Weiss[24] refers to the observation of anginal attacks "regularly" following coitus.)

The pain, he said, seemed to take the form of the letter *S*, with which his first association was that the name of the girl with whom he had had his guilty affair also began with *S*. This also gave rise to a train of thoughts suggested by the words "sin," "sick," "sorry," "sex," "syphilis," etc. He also noticed that having confessed the details of this episode the heart symptoms disappeared for a time. They came back, of course, and it was many months afterward that the deeper meaning of his heart attacks was discovered. This occurred as follows:

For several weeks he had been very much more able than usual to deliver free associations and less obliged to harangue the analyst as was his wont about his heart,

his selfish wife, the futile and endless psychoanalysis, etc. Then one day he reported the following dream which threw light on his reiterated complaints of pain in the heart, with fear of death, etc.

The dream was short. It was only that *"Sammy" Insull was there and had died or was about to die on account of heart trouble and the cause of it was an obstruction in his heart which seemed like a blocked valve in a carburetor.*

His associations to the parts of the dream were: "Insull is a persecuted man; they have just smoked him out of Greece and brought him back to this country, but it is only because the politicians want to save themselves. They say he is a rascal, but I sympathize with him. Perhaps I identify myself with him because I am hounded. [And because you have heart trouble?] Yes, he is sick, and I am sick. [But what is he charged with?] With taking other people's money. With trying to get everything he could get his hands on, I guess."

It was pointed out to the patient that he minimized the charges against Insull of having misused funds, misrepresented facts, and taken so much from so many people. In this sense the identification was quite clear. The patient felt guilty on account of his own grasping, stealing, sucking propensities, and defended these propensities in Insull with whom he identified himself. In the dream he called Insull "Sammy" which bespoke a friendliness and intimacy which he rarely assumed with anyone except himself. The carburetor, as he said, is the intake organ for the automobile and represented his own sucking mouth. Carburetors suck in air and gasoline, and this sucking was blocked, and it was (in the dream) this blocking that was breaking down the heart.

In order to get a complete idea of the case it would be necessary to summarize the whole life history, and, as this would be a practical impossibility, we shall content ourselves by saying that he had been an "oral character" all his life; that is to say, the thwartings of his childhood had been such as to greatly sharpen his appetite for love and this love which he demanded and obtained from many people or at least wanted to do so. It is important in this connection to mention that he was not weaned by his mother until he was almost three years old, and as he said himself, "I can see that emotionally I was *never* weaned." He betrayed this peculiarity in many ways as well: sucking and puckering up his lips, smoking and chewing excessively and talking and arguing a great deal. Whenever he would approach a realization of certain more socially reprehensible activities such as fellatio, he would go into great panic, deny them absolutely (before he had even been accused), sulk, and denounce psychoanalysis; but, on the other hand, at such times the heart symptoms would be gone.

The implication of the above dream is, with this background, quite intelligible, even to one whose experience with dreams is relatively limited. His unconscious is trying to say in picture language something like this: "Sam Insull is like me. He is a great man, but he is persecuted. Like me he is utterly disappointed. He tried to get everything, and lost. I, too, feel disappointed and guilty. The pain in my heart represents a punishment for this guilt and also represents my disappointment in the blocking of my intaking capacity (carburetor)."*

CASE 3.—A third case, which we present through the courtesy of Dr. Edwin Eisler, of Chicago, was that of a man, forty-one years of age, who was engaged in an active law practice. His chief complaint was periodic precordial heart pain, with radiating pain down the left arm. These attacks at first seemed to be related to slight effort but were later noted to be unassociated with any specific activity. The

*Dr. Leon Saul, of Chicago, informed us upon reading this case that he had had one so nearly identical in many respects that the case history would sound almost like copy. This even went so far as to include the identification with Insull, dreams about him, defense of him, etc. In Dr. Saul's case the mechanisms seemed to be quite similar to those reported here, and for this reason, as well as some reasons of professional discretion, it seemed undesirable to give further details of Dr. Saul's case.

patient's father died of angina pectoris, complicated with diabetes, when the patient was twenty years of age, and had also been known to have several attacks of depression in his later years. The mother was living and well, and described as a high-strung, severe, patriarchial type.

The patient was the oldest of three children, with a brother, now quite successful, nine years younger, and a sister eleven years younger. As a child the patient was of a delicate constitution, but at thirteen years of age he began athletic training. This he carried on in college and excelled in it. He was of superior intelligence and barely missed election to the honorary scholastic fraternity because of time spent on athletics. He had never made a conspicuous success in his business and in fact at times had had to receive financial aid from his mother. He attributed his lack of success to his scrupulous honesty and overconscientiousness.

At the age of twenty-five years, he married an aggressive woman, in many respects similar to his mother. They had two daughters aged fourteen and sixteen years at the time of this study. The patient's sexual life had been eccentric, with numerous outside heterosexual contacts; his relations with his wife had never been satisfying to her. He had always been extremely critical of his wife and unconsciously had displayed an aggressively hostile attitude toward her, which the psychoanalytic data indicated to be a defense of a deeper passive receptive attitude.

His cardiac symptoms began immediately following his wife's recovery from a pelvic operation which was complicated by a severe hemorrhage. The patient himself went to the hospital for examination of his heart and there various physical, electrocardiographic and roentgenographic studies ruled out organic disease.

In the course of his psychoanalytic treatment, it became quite clear that the patient was extremely dependent upon his mother but fundamentally hostile toward her. This attitude had been greatly accentuated by the birth of his brother. The aggressive attitude toward his wife was a carry-over of a similar attitude toward the mother. The mechanism of his defense seemed always to have been the projecting of his aggressive desires on to others, originally the father (i.e., "It is my father that mistreats his wife, not I"). The cardiac pain established and reinforced this identification with the father and simultaneously served as a self-punitive measure for the sense of guilt precipitated by his wife's operation. For example, it was discovered in the course of the treatment that the patient's pain on walking up an incline occurred only on the particular incline of the street leading up to his mother's house.

In this case, then, the cardiac symptoms were definitely associated with an emotional situation, although the patient himself was quite unaware of the connection—an identification with a father who had heart trouble, and a guilt-relieving device on account of deep hatred for his mother. This corresponds very closely, as will be noted, to our second case, above.

When the first draft of this paper was read before the Chicago Psychoanalytic Society, April 27, 1935, Dr. Thomas M. French in discussion mentioned several similar cases which had come under his observation in the course of psychoanalysis, particularly a man who had had anginal attacks and extrasystoles whose father had died of heart disease. The patient's cardiac neurosis came on at the same age as that of his father at the time of his death. Another case seen by Dr. French was a woman with coronary sclerosis who had suicidal impulses which were definitely shown to be reflected from her hostility toward her mother and in this case the heart disease seemed to serve as an unconscious gratification of these suicidal impulses. Dr.

Franz Alexander also cited some cases psychoanalytically studied, one of which was of particular interest because of the paradoxical outcome.*

Summary of Psychoanalytic Observations.—The psychoanalytic studies of cardiac cases are too few for us to come to any definite conclusions, but some suggestions from the cases reported above might be crystallized around the following outlines.

It would appear that heart disease and heart symptoms are (sometimes) a reflection of strongly aggressive tendencies which have been *totally* repressed. Characteristically they appear in a man who was strongly attached emotionally to his father and often more or less definitely hostile to his mother. The conscious affection for the father completely obliterated the deeply buried hostilities for him. If, then, the father has heart disease or symptoms of heart disease, it is very typical for the patient to include these symptoms in his identification with the father but to carry out the inexpressible patricidal impulses reflexively by unconscious focal suicide. It has been suggested by some of the analysts who have studied these cases that this identification is not with the father so much as with the father's preferred love object, i.e., his wife, the patient's mother, and that in this sense the heart disease is at the same time symbolic of the "broken-heartedness" of disappointment and of the womb, i.e., the internal sex organ of the woman. At any rate, that the aggressive tendencies seem to be important in the development of heart affections is supported by the fact that coronary sclerosis is so enormously more prevalent among men than among women.

These speculations must not be construed to be other than a most tentative hypothesis with which to compare further observations and upon which to base only some projects for specific research investigations.

SUMMARY

We have attempted to show that the emotional factors which tradition and clinical experience alike ascribe to the heart and particularly to disorders of the heart are capable of more explicit designation. Opportunity for cooperative research between cardiologists and psychoanalysts is lacking and is sorely needed. We have presented here some opinions, some intuitions and some case observations. We have

*This patient was a forty-year-old physician, himself a heart specialist! He suffered from a phobia with the definite content of fainting or dropping dead if he were alone—especially on the street or when he left home to visit his patients. In such situations he had attacks of fear connected with palpitation and precordial anxiety. His phobia interfered with his practice to an increasing degree so that his wife had to accompany him on his visits to patients.

Psychoanalysis revealed an extreme longing for and regression to the infantile period in which he could not yet walk and had to be led by his hand. The analysis of one and one-half years succeeded in overcoming his fear to a great extent. He was able to resume his practice and was successful in it again for a period of two or three years after the end of the analysis. Then one day while walking on the street he dropped dead, and the post-mortem examination showed the presence of *organic* heart trouble!

even hazarded a very tentative hypothesis relating to the deeper psychology in some forms of heart disease. Our data are entirely insufficient to prove anything; they only suggest that these psychological factors are sometimes of importance in the development of cardiac pathology. Whether they act by way of bringing about a disordered function which in turn becomes established as organic pathology or in some more direct way, we have no evidence or opinion. The therapeutic effect on the patient of the psychological investigation is also to be regarded thus far as a secondary, though fortunate, corollary of the investigational process.

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THE INCIDENCE OF BLOOD VESSELS IN HUMAN HEART VALVES*

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THE experiments described in this paper were planned for the purpose of determining the incidence of blood vessels in the valves of human hearts which, so far as could be learned from clinical histories and clinical evidence, were free from endocardial disease and its common precursor, rheumatic fever. We assumed that the valves in such hearts would be within normal limits. The work had scarcely got under way, however, before it was observed that some of the valves bore scars of various kinds and, in a few, unmistakable evidence of active or healed valvulitis was present. This report deals with the frequency of occurrence of blood vessels in human heart valves and with the relationship of those vessels to various scars and lesions which were encountered.

Since the middle of the last century when Luschka[1] first described blood vessels in human heart valves, there has been controversy concerning their existence and their significance when present. Luschka believed that all atrioventricular and semilunar valves were vascularized normally. Several years later Rosenstein[2] confirmed Luschka's work while Joseph[3] and Cadiat[4] denied it. Another group of workers, Kölliker,[5] Henle,[6] Frey,[7] Sappey,[8] Cruveilhier,[9] and Coen[10] admitted the presence of blood vessels in the atrioventricular valves, but denied Luschka's claim of their existence in normal semilunar valves. Langer,[11] on the other hand, observed vessels in diseased valves only and not once in a normal valve. He was the first to point out that, in the atrioventricular valves of adults, blood vessels extended only so far as there was muscle, but that in fetal hearts and those of newborn children the muscle fibers and vessels passed to the free edge of the valve and regressed with age. Later, Darier,[12] Königer,[13] Odinzow,[14] Nussbaum,[15] and Tandler[16] supported the main conclusions of Langer.

Rappe[17] described the architecture of vessels in the mitral valve particularly and because of some constancy in structure he suggested the possibility of some vessels being of noninflammatory origin. He also recognized the frequent coexistence of valvulitis.

Köster[18] was the first to suggest the embolic origin of valvular endocarditis and his theory was later supported by Rosenow.[19]

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In more recent years MacCallum[20] demonstrated vessels in the basal third of the atrioventricular valves in dogs. In human hearts Bayne-Jones[21] found vessels in the valves of three of a series of fourteen grossly normal hearts. He also found a richer vascularization of the valves of pigs' hearts. Gross and his coworkers,[22, 23, 24, 25, 26] (1921-1928), using barium sulphate gelatin as an injection mass, succeeded in injecting blood vessels in at least one of the valve leaflets in 18 per cent of a series of 700 human hearts. After a careful clinical and pathological study, however, they considered only 2 per cent—fourteen hearts—of the injected specimens normal. More recently[27] these workers have stated that, if blood vessels do occur at all in human heart valves, they are most infrequent.

Kerr and Mettier[28] and Kerr, Mettier, and McCalla[29] have obtained the highest percentage of injection of heart valve vessels reported to date. These workers used India ink and demonstrated the presence of capillaries in one or more valves of 36 per cent of twenty-eight normal human hearts. Moreover, they found vessels in every instance in 242 pig hearts and five beef hearts. They feel that their results are in harmony with the embolic origin of valvular endocarditis. Wearn[30] in 1928 demonstrated a rich capillary supply in the atrioventricular and semilunar valves. A preliminary report* of the present study was made in 1930.

It is obvious, therefore, that no agreement exists in the literature at the present time as to the frequency of occurrence of blood vessels in the heart valves or whether they ever occur in normal valves. Some of the lack of agreement in the results reported may be accounted for by the difference in the type of hearts selected for study, but a more probable explanation may be found in the wholly different methods employed by the various workers in injecting the vessels in the valves.

In this study one hundred human hearts were used, which were obtained from consecutive necropsies after the elimination of all cases with any history or clinical evidence of endocarditis either in the past or during the final hospital stay. Neither was there any history or evidence of rheumatic fever or allied conditions. Arteriosclerosis appeared in the diagnosis in twenty cases. Of these, fourteen were recorded as having "chronic myocarditis," supposedly due to sclerosis of the coronary arteries, and five died of heart failure. With but two exceptions all those patients with "chronic myocarditis" were over sixty years of age. The most common primary causes of death were respiratory diseases including pulmonary tuberculosis, malignant growths, cerebral hemorrhage, sequelae to surgical operations, and accidents.

METHOD

The method of injection used in our work was as follows: Immediately after each heart was received, it was washed and massaged gently in order to remove as much blood as possible from the coronary vessels. It was then kept moist in the

*Bromer, A. W., Zschiesche, L. J., and Wearn, J. T.: J. Clin. Investigation 7: 487, 1929. Tr. Am. Clim. & Clin. Assoc. 47: 1, 1931.

ice box for twenty-four to forty-eight hours to allow the rigor mortis to pass off. In a few instances the hearts were three or four days post mortem when injected. Immediately before injection the heart was placed in water at about 38° C. and gently massaged until completely free from rigor. Cannulas were tied into the coronary arteries and connected by a Keyes stopcock with a suction apparatus on one side, and on the other with a bottle containing the injection mass (Fig. 1). Suction was applied to the arteries in order to remove as much air as possible and then by a turn of the stopcock, India ink was injected at a pressure of 220 mm. of Hg when the hearts were from adults, and 120 to 150 mm. of Hg in children's hearts. Freshly opened Weber's India ink diluted with an equal part of distilled water proved to be a satisfactory injection mass and easily penetrated the capillaries. During the injection, the heart was massaged while immersed in a tank of 0.85 per cent saline solution at a temperature of 38° C. As far as possible, all leakage from the extracardiac branches of the coronary arteries[31] in the cut edges of the pericardium and around the great vessels was controlled with hemostats.

After injection was completed, the hearts were carefully examined grossly for endocardial, myocardial, and pericardial changes. They were placed in 10 per cent aqueous formalin for fixation. The valves with their rings were removed by dissection and cleared by the Spalteholz method.[32] After clearing, the valves were studied

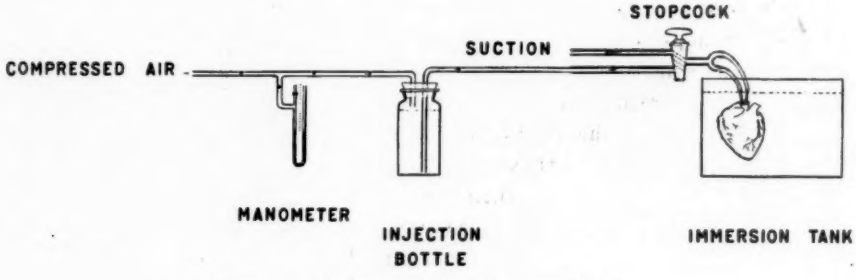

Fig. 1.—Diagram of injection apparatus.

grossly and then submitted to examination with a binocular biobjective microscope in a careful search for blood vessels. This procedure revealed vessels in many instances which had not been visible previous to the clearing. Sections were later taken from various places in many of the valves and from the myocardium of each heart. Those valves which appeared wholly normal on careful gross inspection, showing no scars or thickening, were not sectioned in every instance. Hemotoxylin and eosin, Mallory's connective tissue, and van Gieson's stains were used in staining sections for study.

BLOOD VESSELS IN HEART DISEASE

In this work a valve was considered as having blood vessels in it only when the vessels extended clearly beyond the valve ring into the free portion of the leaflet or cusp. This free portion of the valve is, strictly speaking, the true valve, inasmuch as it is the part that prevents the backflow of blood. In some instances, muscle fibers extended into the free valve, but when they extended well into the free portion they were considered as part of the valve. In no instance did any of our sections include the valve ring as outlined in the text figures by Gross and Kugel.[27] Indeed, we considered the ring as ending at a line drawn

transversely or perpendicularly across the main axis of the valve at the most distal point of its basal attachment. Using this standard, we found blood vessels in one or more valves in eighty-six of the one hundred hearts studied. After completing the microscopic studies, however, twelve hearts showed evidence of valvulitis, either active or healed. In the remaining eighty-eight hearts, gross and microscopic search failed to reveal any evidence of healed or active inflammation. It is possible that in the past there may have been valvulitis that healed without scar formation, or with eventual disappearance of the scar. The absence of inflammatory changes at the time of death, therefore, is not conclusive evidence that a valve has been free from disease. In the twelve hearts with evidence of active or healed valvulitis, the mitral valve was the seat of the lesion in nine instances, and the aortic valve in the other three. Only six of the mitral valves were vascularized, and no blood vessels were found in the aortic valves. Thus, six of the twelve diseased valves were avascular.

Blood vessels were found in the leaflets of one or more valves in seventy-four of the remaining eighty-eight hearts. The number of valves in each heart showing injected vessels varied as follows: In seven hearts, all four valves were injected; in sixteen hearts, vessels were demonstrated in three valves; twenty-six hearts had injected vessels in two valves, while in the remaining twenty-five hearts a single valve showed injected vessels. In twelve valves, uninjected vessels were found by microscopic examination.

The frequency of occurrence of blood vessels in each of the valves is shown in Table I.

TABLE I

EIGHTY-EIGHT HEARTS WITHOUT VALVULITIS

VALVE	VASCULARIZED VALVES	
	NUMBER	PER CENT
Mitral	68	65.9
Tricuspid	65	63.6
Pulmonary	25	28.4
Aortic	14	15.9

The distribution of the vessels varied greatly in the different valves, and there was no uniform arrangement in the individual leaflets. For this reason, the findings in each valve will be presented separately.

MITRAL VALVE

The vessels in the mitral valve were located just beneath the endocardium on the superior surface of the leaflets. Small arteries, arterioles, capillaries, and veins were found in this region. Infrequently one found vessels running up the papillary muscles and through the chordae tendineae to pierce the valve leaflets and anastomose with those on the superior surface. Such vessels almost always occurred in the shorter

papillary muscles and chordae tendineae which were attached to the inferior surface of the valve near its base. Veins extending several millimeters below the basal margin of the aortic leaflet were found in several specimens which were injected under low pressure through the coronary sinus.

The various types of distribution of the vessels encountered in the leaflets are shown in Figs. 2, 3, and 4, which are photographs of mitral valves. The most common arrangement is that shown in Fig. 3 where the vessels extended from 3 to 7 mm. beyond the edge of the ring into the

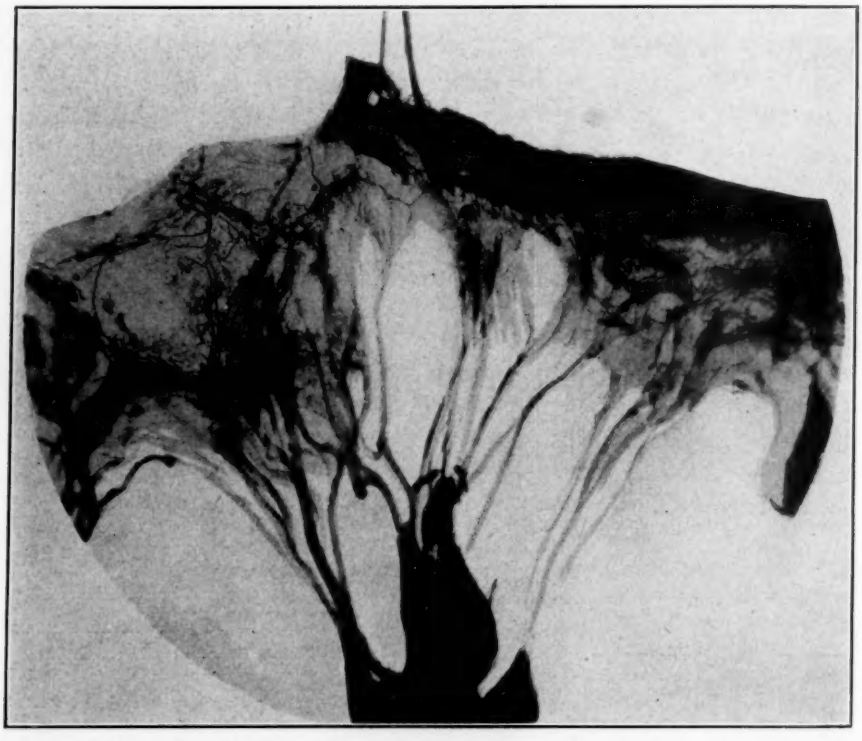

Fig. 2.—H-4-B. Normal mitral valve from subject aged fifty-three years. Magnification ×2.

free leaflet in a rich network of fine caliber as shown in this figure. Many of these small vessels ended blindly, showing that their complete course had not been outlined by the injection mass. This type of distribution was found in less than half of the valves. The other extreme with a rich vascular supply from several arterioles is shown in Fig. 2 on the aortic leaflet. All stages between these two extremes were found.

Less commonly, two small arteries descended from the base of the aortic leaflet along or near the lateral margins to meet near the line of closure. They gave off branches en route, some of which formed delicate anastomoses with other vessels and at times reached the free margin of

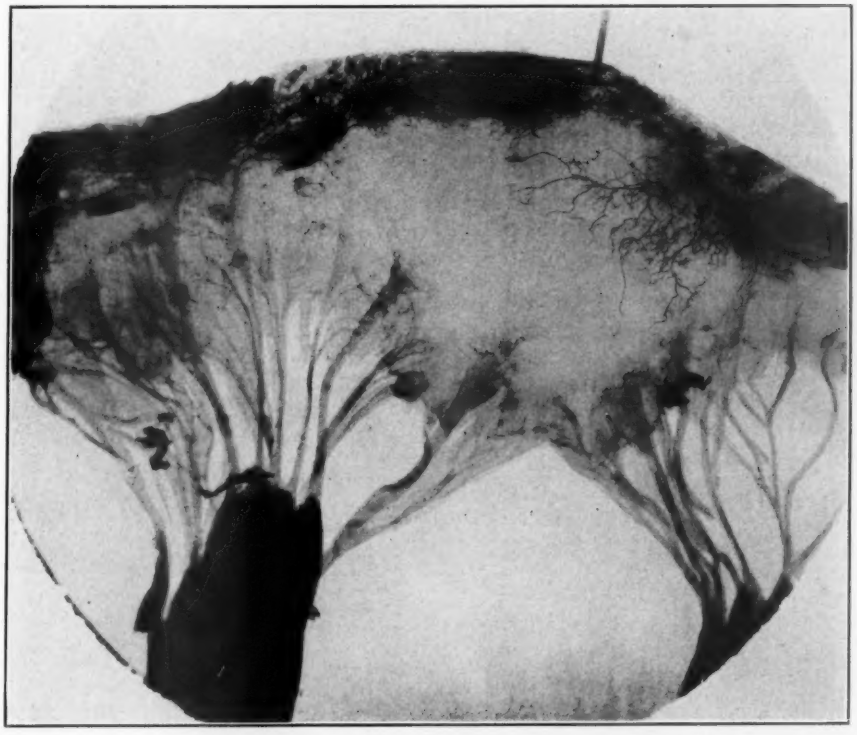

Fig. 3.—H-47-B. Normal mitral valve from subject aged fifty-eight years. Magnification ×3 (approximate).

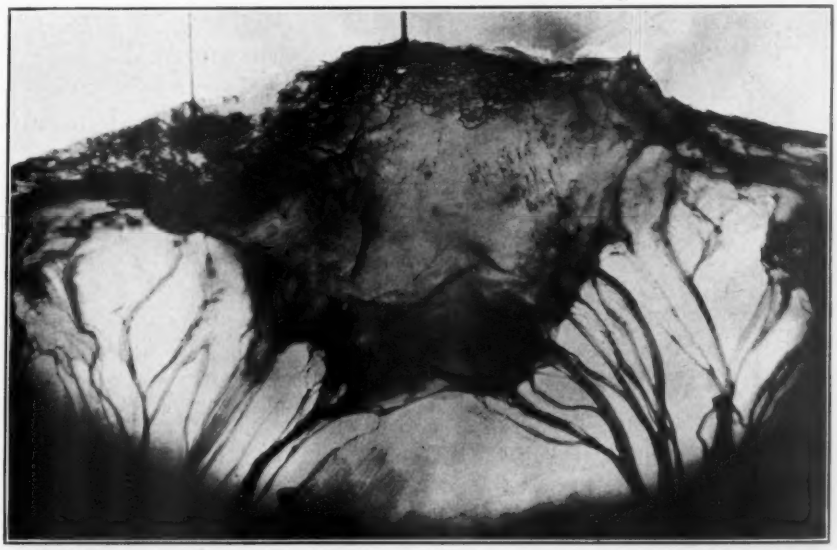

Fig. 4.—H-105-B. Normal mitral valve from subject aged fifty-five years. Magnification ×3.

the valve. There was no constant distribution of the vessels on either leaflet and the relative frequency of occurrence of vessels was approximately the same in the two leaflets.

TRICUSPID VALVE

The vessels of the tricuspid valve were, as a general rule, of finer caliber than those in the mitral. Many of them were not found until the valve had been cleared. In about 40 per cent of the vascularized tricuspid valves, the vessels extended from the base to about one-half the distance to the free margin, while in the remaining ones the vessels were a few millimeters in length. The distribution of the vessels was even less constant than in the mitral valve (Fig. 5).

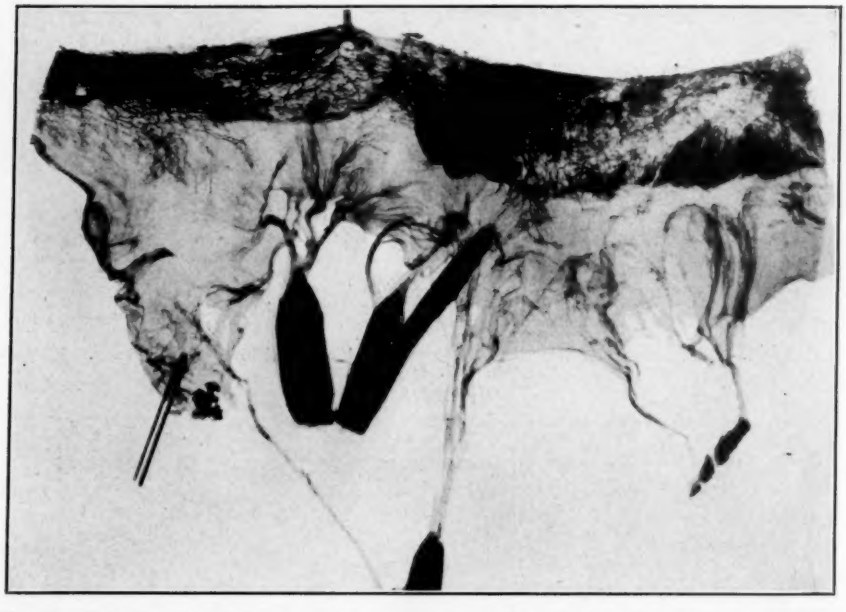

Fig. 5.—H-71-B. Normal tricuspid valve from subject aged fifty-six years. Magnification ×2.

PULMONARY VALVE

In the pulmonary valve, the arteries were of extremely fine caliber. They emerged from the line of attachment of the valve at numerous points, sometimes from the commissures between the cusps and at other times from the base (Fig. 6). The arteries immediately branched into a meshwork of capillaries, the distribution of which was limited for the most part to the lower two-thirds of the cusps. In no instance did they extend to the corpus arantii. Muscle fibers were found rarely in this valve. Vessels were found in one cusp only in seventeen valves, in two cusps in seven instances, and in a single heart all three cusps contained blood vessels.

AORTIC VALVE

In the aortic valve the vessels were, in many instances, of larger caliber than those in the pulmonary valve. They arose as branches of the arteries in the richly vascularized commissures and entered the cusps

Fig. 6.—H-78-B. Normal pulmonary valve from subject aged eighty-four years. Magnification ×4.5.

to extend horizontally across them, at times along the line of closure and, in some instances, reaching the corpus arantii (Fig. 7). No muscle fibers were found in any of the sections examined microscopically. In twelve specimens, the vessels were limited to one cusp, in one specimen to two cusps, and in one heart all three cusps showed injected vessels.

RELATION TO AGE

It is interesting to note the relative incidence of vascularized valves in the various decades of life. This is shown in Table II.

It should be pointed out that the technic for injection of infant hearts is less satisfactory than that for adults in that the coronary arteries are so small that cannulation of them is not practical and the injection must be made through a cannula in the aorta. This fact may account for the lower percentage of injected vessels in the first decade. Otherwise, the incidence of vascularized valves in hearts is essentially the same in all decades. In the first decade, the ages of the individuals whose heart valves contained blood vessels were two days, seven days, nineteen months, three years, four years, and five years.

In view of the former contention of Gross and Kugel and others that the presence of blood vessels in a heart valve predisposes to valvulitis,

TABLE II

INCIDENCE OF BLOOD VESSELS IN NORMAL VALVES IN DECADES

AGE PERIOD	NUMBER OF HEARTS INJECTED	NUMBER HEARTS WITH VASCULARIZED VALVES	PER CENT
First decade	11	6	55
Second decade	2	2	100
Third decade	10	7	70
Fourth decade	9	7	78
Fifth decade	12	12	100
Sixth decade	24	20	83
Seventh decade	10	10	100
Eighth decade	5	5	100
Ninth decade	5	5	100

it is interesting to compare the frequency of occurrence of blood vessels in a valve to the incidence of endocarditis in that valve. It is generally accepted that the mitral valve is the most common seat of endocarditis and that the aortic, tricuspid, and pulmonary valves follow in the order named. Endocarditis in the pulmonary valve is a relative rarity although, as shown by Holsti[33] and Swift,[34] careful microscopic study may reveal the presence of inflammation when gross evidence of such is lacking.

The mitral valve, the most frequent site of valvular endocarditis, shows practically the same incidence of vascularization as the tricuspid valve. Aside from the mitral valve, there is no further agreement between the frequency of occurrence of blood vessels and the incidence of valvulitis in a given valve. In the aortic valve, for instance, which stands next in frequency to the mitral as a site of valvulitis, blood vessels were encountered less frequently than in any other valve. The surprisingly high incidence of blood vessels in the tricuspid valve, which, indeed, is practically as high as that in the mitral, is of great interest, for the incidence of endocarditis in this valve is considerably less than in the

mitral. Finally, the presence of vessels in twenty-five out of eighty-eight pulmonary valves is out of all proportion to the incidence of endocarditis in this valve. The clinical occurrence of pulmonary valvulitis is rare, and acceptable microscopic evidence of its presence is uncommon.

Such gross lack of agreement in the incidence of blood vessels and valvulitis in a given valve is suggestive evidence that the mere presence of blood vessels does not predispose to valvulitis. This evidence is of greater import if the vessels occur normally in the valves, for in that event endocarditis, if embolic in origin, should occur with the same frequency approximately as do the vessels in the valve. But evidence of this sort is not conclusive, even though strongly suggestive.

A great many scars of a noninflammatory nature were found in the routine examination of the valves. Grossly, they appeared as a simple

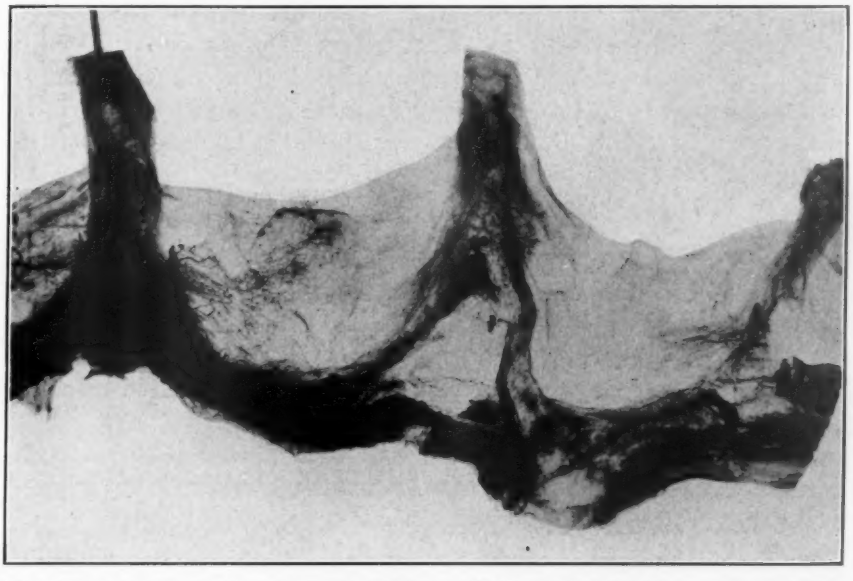

Fig. 7.—H-4-B. Normal aortic valve from subject aged fifty-three years. Magnification ×2.

thickening in the valve or as sclerotic plaques. These scars were both proliferative and degenerative, but in neither was there any evidence of inflammatory change. The proliferative scars showed myxomatous, fatty or hyaline degeneration, while the degenerative ones were the same but without signs of any earlier proliferation. In many instances, the thickened area was poorly defined and appeared as a simple thickening of the normal layers of the valve. Both types, when present, occurred at almost any point on the valves, at the base near the ring, in the midportion, or on or near the free edge. They were found in the valves with and without blood vessels and when vessels were present they appeared to bear no relation to the scars. On many vascularized valves no scars were found. We have interpreted these scars as signs of the

wear and tear of life because we have been unable to discover any evidence of healed or active inflammation in them.*

DISCUSSION

The occurrence of blood vessels in the valves of seventy-four out of eighty-eight hearts represents a much higher incidence than any previously reported. When one considers that all the patients from whom the hearts were obtained gave no clinical evidence of endocarditis, but died of other diseases, the findings seem to indicate that blood vessels occur normally in human heart valves. The occurrence of numerous scars on the valves, however, raises the question of previous valvulitis. Our studies show that in many instances the scars and the vessels were unrelated, and the incidence of vessels in a given valve did not correspond to the incidence of valvulitis in that valve. Moreover, there was no microscopic evidence of active or healed valvulitis in any of the seventy-four hearts. If the vessels are of inflammatory origin in the seventy-four hearts which we have included as normal, it would indicate that about 84 per cent of normal people have had unrecognized endocarditis at some time in their lives. If the vessels are not of inflammatory origin, as our studies suggest, one must accept the fact that blood vessels occur normally in human heart valves.

SUMMARY

1. In one hundred hearts from patients without history or clinical evidence of endocarditis, blood vessels were demonstrated in the valves of eighty-six.

2. Twelve of the hearts showed evidence of active or healed valvulitis on one or more valves.

3. Active or healed valvulitis occurred in the absence of blood vessels, and blood vessels were found in valves without evidence of active or healed valvulitis.

4. Of the eighty-eight hearts without evidence of previous inflammation, blood vessels were found in one or more of the valves in 84 per cent.

5. The incidence of blood vessels in a given heart valve was not in keeping with the incidence of rheumatic valvulitis in that valve.

6. A method of injecting the blood vessels in heart valves is described.

The authors wish to express their thanks and appreciation to Professor F. B. Mallory, Dr. Frederic Parker, Jr., and Dr. A. R. Moritz, all of whom gave generously of their time and were most helpful with their criticisms.

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*A more detailed study is being made on a series of four hundred human hearts in which the blood vessels in the valves have been injected; and will be published soon.

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NOTES ON CARDIAC PAIN AND CORONARY DISEASE

Correlation of Observations Made During Life With Structural Changes Found at Autopsy in 476 Cases*†

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THE mechanism by which painful impulses are initiated in the heart is, as yet, but imperfectly understood. There is much evidence in support of the current belief that the most important predisposing cause is relative ischemia of the myocardium.[1] The commonest, though not the sole condition leading to a deficient supply of blood to the heart muscle, is impairment of the coronary circulation. In these notes, an attempt is made to define some of the clinical and pathological features of coronary disease which are associated with cardiac pain and which appear to favor its occurrence. At this time, only certain general statements are made. More detailed study of various aspects of the subject will be reported later.

MATERIAL

The cases were assembled from the files of the Department of Pathology‡ in much the same manner as described in an earlier paper.[2] The twelve-year period from 1918 to 1929, inclusive, was chosen because the work was begun in 1930 and the clinical records prior to 1918 often failed to contain the information desired. Each protocol indexed under the following headings was examined: arteriosclerosis of the coronary arteries, thrombosis of a coronary artery, infarct of the myocardium, aneurysm of the heart, fibrosis of the myocardium, embolism of a coronary artery, occlusion of the coronary arteries, syphilis of the aorta, stenosis of the orifice of a coronary artery, rheumatic coronary arteritis, rheumatic aortitis and generalized arteriosclerosis. Particularly under this last caption were found numerous cases showing the lesser grades of coronary sclerosis and not included in the diagnostic files as coronary disease. A detailed analysis was made of 476 cases showing lesions in the coronary arteries or the aorta. Both clinical and pathological findings were recorded on special charts. The cases were divided, for purposes of study, into four etiological groups as shown in Table I, namely, arteriosclerosis, syphilis, rheumatic fever, and miscellaneous. The observations

*From the Department of Medicine, College of Physicians and Surgeons of Columbia University, and the Medical Clinic of the Presbyterian Hospital.

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‡The writers are indebted to the Department of Pathology (Dr. J. W. Jobling, director) for permission to utilize these records.

made during life were correlated with the structural changes noted at autopsy. Cardiac pain was the central point of interest about which the other features were grouped, and only such facts are here presented as bear upon the presence or absence of painful discomfort. Because of the relatively small number of records, the results of the analysis are to be regarded as applying to this particular group of patients and not necessarily as generalizations.

FACTS NOTED

General Observations.—From Table I it is apparent that:

1. Cardiac pain occurred in the presence of a few scattered intimal plaques in the coronary arteries, as well as when many were found. Even calcification of the artery or narrowing of the lumen did not increase the

TABLE I

INCIDENCE OF CARDIAC PAIN IN 476 CASES WITH VARIOUS LESIONS

ETIOLOGICAL GROUP	TOTAL NUMBER OF CASES	PAIN PRESENT (PER CENT)
A. Coronary arteriosclerosis		
1. Few to many plaques	201	20
2. With calcification or stenosis	103	23
3. With arteriosclerotic occlusion	34	44
4. With thrombosis	33	39
B. Syphilitic aortitis		
1. Coronary mouths not involved	14	0
2. Coronary mouths narrowed or occluded	7	86
3. Coronary mouths not involved; coronary sclerosis present	32	22
4. Coronary mouths narrowed or occluded; coronary sclerosis present	11	64
C. Rheumatic fever		
1. Coronary arteritis	3	33
2. Aortitis; no coronary involvement	12	25
3. Aortitis; coronary sclerosis present	16	50
D. Miscellaneous	10	70

incidence. This observation suggests the inference that irritation in the wall of an artery or spasm, or both, may be causative factors. It was only when the vessel was actually occluded, either by the arteriosclerotic process or by thrombosis, that the incidence of pain doubled. Thus, pain was present in but 20 per cent of the cases with coronary sclerosis without occlusion, and in 40 per cent of cases with closure of a branch. In Russia, Kudrin,[3] studying 500 cases of coronary sclerosis at autopsy, found narrowing of the lumen in 22 per cent giving a history of anginal attacks and in only 5 per cent of the remainder. Occlusion was noted in 30 per cent of cases with pain and in only 4.6 per cent of those without discomfort. But the conditions which determine the presence or absence of pain in any given instance are not clearly defined.

2. In fourteen cases of simple syphilitic aortitis without coronary involvement, either specific or arteriosclerotic, pain was not noted in a single instance. On the other hand, when the mouths of the coronaries were narrowed or occluded by the syphilitic process, pain occurred in six of seven cases (86 per cent). It may therefore be said that in syphilitic aortitis in the absence of aneurysm, if chest pain is present, there is involvement of the coronary arteries either at their orifices by syphilis, or farther along in their course, by arteriosclerosis. Obviously, these two etiological types of coronary pathology may coexist. It has previously been pointed out that pain is not part of the picture of uncomplicated aortitis;[1a, 4] but this observation has not been sufficiently stressed.

3. In rheumatic fever, of which thirty-one cases were included in the series, pain occurred in association with either coronary arteritis or rheumatic aortitis. More extensive and detailed microscopic study, as made by Karsner and Bayless,[5] will perhaps reveal rheumatic coronary lesions in a higher percentage of cases. In the older rheumatic patients, sclerotic lesions in the coronaries increased the likelihood of the occurrence of attacks of pain.

4. Paroxysmal pain referred to the sternum or precordial area, and simulating that observed in the presence of intrinsic coronary pathology, occurred as part of the clinical picture in a variety of conditions. In the ten cases included in a miscellaneous group were instances of cardiac hypertrophy of unknown etiology, with myocardial lesions; pulmonary arteritis; embolism of a coronary artery; adherent pericardium; syphilitic myocarditis; ball thrombus in the left ventricle with aneurysm of the heart; aortic aneurysm compressing the right coronary artery. In some of these cases the coronary blood flow was impaired; in others a few intimal plaques were found in the coronary vessels. This group serves to emphasize the fact that cardiac pain is observed in association with a variety of pathological states.

The Rôle of Aortic Insufficiency.—Of 474 patients, 415 did not have aortic insufficiency; pain was present in this group in 24 per cent. In the 59 cases with aortic insufficiency, pain was noted in 49 per cent. It appears, then, that patients with aortic insufficiency are twice as likely to have pain as those without it. This is probably due to the lowered diastolic pressure in certain instances, with resultant diminution in the amount of coronary blood flow.[6]

On the other hand, the presence of aortic insufficiency without associated coronary lesions does not necessarily induce discomfort. Thus, in four cases of syphilitic aortitis with aortic insufficiency but without coronary pathology, there was no pain.

Arteriosclerosis of the Coronary Arteries.—This group comprised the greatest number of cases—338. The following observations were made:

1. The ages ranged from twenty to eighty-five years, with averages in the various subgroups shown in Table I, from 51 to 65 years. The milder grades of sclerosis were observed in the younger patients.

2. There were twice as many males as females in the series. Yet the incidence of pain was the same in both sexes, i.e., 23 per cent in males and 24 per cent in females. Marked sclerosis was more common in the males in the ratio of 3 to 1.

3. In the total hospital autopsy series, the ratio of white to negro is 11 to 1. In this series it was 12 to 1. But of 137 cases of advanced sclerosis, 133 were in whites and only 4 in blacks. This is a ratio of 34 to 1. The incidence of pain in the two races was, however, the same (Table II).

The infrequency of the anginal syndrome in the colored race has repeatedly been the subject of comment.[7] One reason for this observation appears to be the fact that advanced sclerosis of the coronary arteries is relatively rare in the negro.

TABLE II

INCIDENCE OF CARDIAC PAIN IN 310 WHITES AND 27 NEGROES IN RELATION TO THE DEGREE OF CORONARY SCLEROSIS

	WHITES		NEGROES	
	TOTAL NUMBER OF CASES	PAIN PRESENT (PER CENT)	TOTAL NUMBER OF CASES	PAIN PRESENT (PER CENT)
Few to many plaques	177	19	23	30
Calcification or stenosis	100	24	3	0
Arteriosclerotic occlusion	33	45	1	0
Total group	310	24	27	26

4. In a previous paper it was pointed out that occupation does not appear to play a significant part in determining those whose coronary arteries are affected by sclerosis.[2] The largest number of patients with coronary sclerosis was found among foremen and skilled workers, but the figures in different occupational groups did not show wide variations. With respect to the occurrence of pain, however, occupation seems to be of real importance (Table III). The highest incidences were found

TABLE III

INCIDENCE OF CARDIAC PAIN IN RELATION TO OCCUPATION IN 311 CASES OF CORONARY SCLEROSIS

OCCUPATION	TOTAL NUMBER OF CASES	PAIN PRESENT (PER CENT)
Housewives	96	29
Manual laborers	88	28
Clerical workers	38	21
Foremen and skilled workers	50	18
Professional men and executives	39	18

in housewives and manual laborers (29 and 28 per cent, respectively). Clerical workers occupied an intermediate position (21 per cent), whereas foremen and skilled workers, as well as professional men and executives, showed an incidence of only 18 per cent.

A somewhat similar set of observations was made by Kleimann,[8] working in Aschoff's laboratory in Freiburg. He, too, noted that in the presence of coronary sclerosis those individuals whose daily work called for physical effort were most likely to experience pain. He found an equally high incidence among those whose occupations, in addition to physical exertion, involved emotional stress. In this latter group he specifically mentions physicians.

That the housewives should occupy such a prominent place in our own series is not surprising if account is taken of the fact that the women who occupy beds in the hospital wards almost invariably do their own housework. Scrubbing, washing, and lifting are integral parts of their daily chores. The character of their activities may well be classed as manual labor.

5. Congestive heart failure was present in 154, absent in 184 cases. Pain was frequent in those patients who gave a history of congestive failure (40 per cent); it was relatively uncommon in those who had not had failure (10 per cent). Conversely, in 80 cases with pain, congestive failure was observed in 78 per cent; in 258 cases without pain, congestive failure was noted in only 37 per cent. In short, in a group of patients sick enough to seek relief in a hospital and eventually to die there, pain was four times as frequent in those who had congestive failure as in those whose myocardial function was well preserved. And congestive failure was twice as common in the patients with pain as in those without it. These figures are undoubtedly influenced by the fact that patients with coronary disease rarely seek bed care for pain alone; they enter the hospital because of cardiac insufficiency. Those without pain were largely instances of latent coronary sclerosis discovered at autopsy in subjects who died of conditions not directly related to the cardiovascular system.

6. The presence or absence of hypertension, in the group as a whole, had no effect on the incidence of pain. But of fifty-one males with pain, 48 per cent had hypertension; of twenty-seven females, 74 per cent had hypertension. There is an association between cardiac pain and elevation of the blood pressure in women. This relationship has previously been noted by Eppinger and Levine[9] who believe that, in females, it may be used as a diagnostic aid in distinguishing pain of cardiac origin from that due to other causes. Although, on the basis of probability, cardiac pain in a woman with normal blood pressure is not due to coronary disease, each individual case must be the subject of special study.

7. Electrocardiograms were taken in 138 cases. Deviations from the normal were found in 120 (87 per cent). The most frequently observed changes were significant T-wave negativity (88 cases); auricular fibrillation (36 cases); ventricular premature beats (33 cases); auriculoventricular block (24 cases) and bundle-branch block (19 cases). Pain was twice as common in the patients with abnormal, as in those with normal, graphic records (44 per cent as against 22 per cent).

8. Cardiac hypertrophy was found in 236 cases (70 per cent). In the patients with hearts of normal weight, 13 per cent had pain; of the group with enlarged hearts, 27 per cent had pain—again a doubled incidence. Furthermore, in the series with hypertrophy the hearts of patients with pain were consistently larger than those without it. The average weights (both sexes) were: with pain, 543 grams; without pain, 505 grams.

9. Fibrosis of the myocardium, gross or microscopic, was present in 204 cases (60 per cent). Pain occurred much more frequently in the presence of fibrosis (31 per cent) than in its absence (12 per cent). In 80 cases with pain, fibrosis was present in 80 per cent; in 257 cases without pain, fibrosis was present in 55 per cent. Kleimann,[8] to whose paper reference has already been made, observed cardiac pain five times as frequently in patients whose hearts at autopsy showed fibrotic scars as in those whose did not.

Deviations from the normal in the form of the electrocardiogram, cardiac hypertrophy, and fibrosis of the myocardium are all signs of a damaged heart muscle. In the cases under discussion, such damage is the result of impairment of the blood supply.[10] Pain, then, is more likely to be experienced by the person with a damaged myocardium than by one whose heart muscle has not suffered materially from the milder grades of ischemia.

Coronary Thrombosis.—1. Of 33 patients, 2 died in coma within an hour after admission to the hospital, so that no history was obtainable. Of the remaining 31, 12 (39 per cent) had pain with the attack. In a series of 76 cases collected by Davis,[11] in Chicago, there was a history of pain in 47 per cent. Certainly pain is present in less than half of the cases which come to autopsy. If the milder forms described by Levy[12] are taken into account, the incidence is probably even lower than that here given. In our experience, those patients who had no symptoms prior to the acute episode were most likely to have no pain associated with it.

The particular artery occluded was not alone responsible for determining the presence or absence of pain; nor did the occurrence of myocardial fibrosis outside the area of infarction seem to play a part.

2. There was only one negro in this series of 33 cases. The relative infrequency of coronary thrombosis in the colored race is probably directly related to the rarity of advanced coronary sclerosis in the black, as previously noted in this paper.

3. Four patients with cardiac aneurysm had no pain associated with the final acute occlusion. As Herrick[13] has pointed out, the area irrigated by the artery in such cases has become comparatively insensitive due to destruction of vessels, nerves, and functioning muscular tissue, so that a painful response to the new obstruction is not experienced. Under these circumstances, dyspnea, sudden weakness, sweating, or pulmonary edema may be the pain equivalent.

SUMMARY

In these notes, an attempt is made to define some of the clinical and pathological features of coronary disease which are associated with cardiac pain and appear to favor its occurrence. Among the factors considered are the etiology of the coronary lesions; their extent, with particular reference to stenosis or occlusion of an artery or its orifice; the influence of sex, race, and occupation; the relationship between pain and congestive failure; the association with hypertension; the effect of damage to the heart muscle, as shown by cardiac hypertrophy, fibrosis of the myocardium and changes in the form of the electrocardiogram; and the rôle of aortic insufficiency.

All of the conditions which determine the presence or absence of pain in any given instance are not known. But a number of the factors cited are clearly concerned in predisposing to painful discomfort.

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ELECTROCARDIOGRAMS DERIVED FROM ELEVEN FETUSES THROUGH THE MEDIUM OF DIRECT LEADS*

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DURING the course of a routine study of the cardiac mechanisms of premature and full-term infants, we were fortunate in securing a fetus of twelve and one-half weeks' gestation a few minutes after its delivery by hysterotomy. Knowing that electrocardiograms had been obtained from the embryo chick, we endeavored to obtain electrocardiographic curves from this human embryo. In this attempt we were successful. Six months later, on April 14, 1934, the results of this study were reported at a meeting of the Biological Society of the University of Pittsburgh. At that time a search of the literature failed to show that previous attempts had been made to secure electrocardiograms from human fetuses through the medium of direct leads.

Staff positions in a hospital under university control affording approximately 2,400 births annually have provided us with material for a continuance of our study. We have up to this time electrocardiograms from eleven fetuses, eighteen premature infants, and eighty full-term infants. The present report is a preliminary one and will be confined to our observations upon members of the first group. During the course of this communication, we will use the term fetus as applied to those members of the entire group in which the period of gestation varied from 9½ to 25 weeks, estimations of age being based upon Streeter's *Charts of the Human Embryo*.[1]

Of our eleven fetuses, seven were obtained by hysterotomy. With one exception these had been kept totally immersed in warm Tyrode's solution from time of delivery. They were removed from this solution on arrival at heart station. There they were allowed to cool to room temperature. The fetuses which had been delivered spontaneously were not immersed. The placenta was detached from only one of the fetuses which had been removed by hysterotomy. From the others it had been separated at time of delivery. Six of the hysterotomized women had been delivered under spinal anesthesia, one under ether. The mothers who had delivered spontaneously received morphine sulphate only. Neither type of anesthetic or analgesic administered to mothers nor separation from placenta previous to total

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immersion or non-immersion appeared to influence the pattern of the electrocardiograms or the periods of time over which deflections could be recorded.

In all instances a stationary electrocardiograph was employed without resort to amplification. Ordinary copper wire was used for electrodes, with standard hook-up. The fourth lead was obtained in accordance with the technic of Wolferth and Wood.[2] Apparently our difficulties in maintaining accurate standardization throughout the longer periods of observation have had little or no effect upon the results obtained.

We believe that we are justified in reporting the details of our findings inasmuch as we are able to discover at this time but one reference to an electrocardiogram derived from fetus through the medium of direct leads. In October, 1934, or one year after our first electrocardiogram had been obtained, Dr. Mary Easby[3] published an electrocardiogram taken from a fetus of four and a half months' gestation. An attempt to obtain limb leads was successful only in regard to Lead II. Chest leads were recorded, but no statement is made as to which electrode was employed anteriorly.

We are aware, of course, that several reports have been made of galvanometric curves obtained from the fetus in utero.[4, 5] Such studies are of interest but are not strictly comparable with those based upon results obtained through the direct application of the standard technic.

Our observations rest upon analysis of three standard limb leads obtained from all eleven fetuses as well as of fourth lead curves from five of them. Serial electrocardiograms were obtained from four fetuses. In one instance, observation continued to the point at which deflections ceased to appear. In the others, deflections could still be recorded at the time when the subjects were removed from the heart station.

Table I gives a tabulation of our readings.

DISCUSSION

To us, the most interesting outcome of our study was our ability to prove that electrocardiograms can be readily obtained from fetuses by means of the usual technic as applied to all four of the standard leads. We had but one failure in spite of the fact that most of our subjects had been totally immersed for periods varying from seven to thirty minutes before they were available to us.

The persistence of deflections over relatively long periods of time is worthy of comment. In three of the subjects, deflections were still obtainable at periods of 35 minutes, 55 minutes, and 205 minutes after their delivery by hysterotomy. In a fourth fetus deflections ceased

210 minutes after its spontaneous delivery. It is possible that such deflections may represent a passage of the excitation wave without contraction of heart muscle.[6]

The amplitude of the deflections which we recorded in our series was usually somewhat lower than that derived from adult hearts; but occasional exceptions occurred in derivations from limbs while the T-wave as derived from chest lead showed a marked excursion from the isoelectric line.

The initial rate of cycles varied widely: the highest was 100; the lowest, 35. It will be obvious that in all instances, these rates are lower than the audible rates recorded from fetuses in utero. In all of our subjects from whom serial electrocardiograms were obtained, progressive slowing of rate was recorded. Thus, in one fetus the rate fell from 86 to 42 over a period of thirty-five minutes. It is probable that gradual cooling of the fetuses was partly responsible for this slowing of rate.

Left axis deviation was not present in any of the electrocardiograms. In five instances, right predominance was present; in six, no dominance was demonstrated. It is to be noted that in one of the cases in which dominance was not discernible in the first electrocardiogram, a definite right deviation appeared thirty-five minutes later.

The sinus node was dominant in all of our initial electrocardiograms. Slight sinus arrhythmia was present in four. In one subject the A-V node became dominant a short time before deflections ceased.

P_1 was negative in one instance. P_4 was invariably negative where S-A node was dominant. In the one case in which nodal rhythm was established, the previously negative P_4 became positive.

The comparison of the conduction time in the human adult heart with that of the human fetus shows the fetal conduction time to be only slightly shorter. This, in view of the relatively enormous difference in the size of the two hearts, indicates that the excitation wave in the human fetal heart is much slower than the excitation wave in the human adult heart. Studies of the conduction mechanism in the chick embryo and the adult hen have shown this same relationship to be present. An observation in the literature, which is of interest in the consideration of the conduction time, would indicate that the relative size of the heart has but little influence on the speed of the excitation wave. Thus a small bat had a conduction time of 0.03 as compared with a conduction time of 0.30 in an elephant, which was 400,000 times the weight of the bat; a ratio of 10 to 1 in the conduction time as compared with 400,000 to 1 in weight.[7]

Q-waves were not recognized in any of our standard leads.

The primary complexes were monophasic in all limb leads in two of our subjects: it was diphasic in all limb leads in two; it occurred

TABLE I

TABULATION OF READINGS OF ELECTROCARDIOGRAMS DERIVED FROM HUMAN FETUSES THROUGH THE MEDIUM OF DIRECT LEADS

	NO. 1 9½ WK. A	NO. 2 11½ WK. A	NO. 3 12½ WK. A	NO. 4 13 WK. A	NO. 5 14 WK. A	NO. 6 14 WK. A	NO. 7 22 WK. A	NO. 8 18 WK. B	NO. 9 18 WK. B	NO. 10 22 WK. B	NO. 11 25 WK. B
Rate	90-50	48	80	92-80	90	90 80 60	86-42	45-22	35-29	60	100-92
Rhythm	Irreg. Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Irreg. Sinus	Irreg. Sinus	Sinus	Irreg. Sinus
P-I	Iso.	Iso.	Neg. M.V. 1∓	Pos. M.V. 1∓	Pos. M.V. 1∓	Iso.	Pos. M.V. 1∓	Pos. M.V. 2	Pos. M.V. 2∓	Pos. M.V. 1∓	Pos. M.V. 1
P-II	Invert Iso. Pos.	Pos. M.V. 2∓	Iso.	Pos. M.V. 1∓	Pos. M.V. 1∓	Pos. M.V. 2∓	Pos. M.V. 1∓	Pos. M.V. 2∓	Pos. M.V. 1∓	Pos. M.V. 3	Pos. M.V. 1∓
P-III	Iso.	Iso.	Iso.	Iso.	Iso.	Pos. M.V. 1∓	Neg. M.V. 1∓	Pos. M.V. 2	Iso.	Pos. M.V. 1∓	Pos. M.V. ½∓
P-IV		Invert M.V. 1∓					Invert M.V. 2∓		Invert M.V. 2∓	Invert M.V. 2	Invert M.V. 1
Axis deviation	No	Right	No	Right	No	Right	No	Right	No	Right	No
T-I	Iso.	Iso.	Neg. M.V. 1∓	Pos. M.V. 1∓	Pos. M.V. ½∓	Pos. M.V. 2∓	Pos. M.V. 1∓	Pos. M.V. 2	Iso.	Pos. M.V. 2	Pos. M.V. 1∓
T-II	Diph.	Iso.	Neg. M.V. 1∓	Pos. M.V. 1∓	Pos. M.V. 1∓	Pos. M.V. 2∓	Pos. M.V. 1∓	Pos. M.V. 2	Iso.	Pos. M.V. 1∓	Pos. M.V. 1

TABLE I—CONT'D

	NO. 1 9½ WK. A	NO. 2 11½ WK. A	NO. 3 12½ WK. A	NO. 4 13 WK. A	NO. 5 14 WK. A	NO. 6 14 WK. A	NO. 7 22 WK. A	NO. 8 18 WK. B	NO. 9 18 WK. B	NO. 10 22 WK. B	NO. 11 25 WK. B
T-III	Iso.	Iso.	Neg. M.V. 1∓	Diph.	Iso.	Pos. M.V. 1∓	Neg. M.V. 1∓	Diph.	Iso.	Invert M.V. 1∓	Iso.
T-IV		Pos. M.V. 3					Pos. M.V. 3∓		Pos. M.V. 3∓	Pos. M.V. 6	Invert M.V. 2½∓
ST-IV		Sl. High Take Off					Sl. High Take Off		Iso.	Sl. High Take Off	Sl. High Take Off
Conduction time	0.12	0.10	Lead I 0.16	0.12	0.10	0.12	0.12	0.12	0.11	0.12	0.12
QRS-I	Diph. M.V. 2∓	Mono. M.V. ½∓	Mono. M.V. 1∓	Mono. M.V. 2	Mono. M.V. 1∓	Mono. M.V. 2∓	Diph. R-4 M.V.	Diph. S-5 M.V.	Diph. R-4 M. V.	Diph. S-3 M.V.	Diph. R-3 M.V.
QRS-II	Diph. R-2 M.V.	Mono. R-2 M.V.	Mono. 3 M.V.	Mono. R-5 M.V.	Mono. R-2 M.V.	Mono. R-3 M.V.	Diph. R-6 M.V.	Mono. R-8 M.V.	Diph. R-3 M.V.	Diph. R-5 M.V.	Diph. R-5 M.V.
QRS-III	Diph. R-2 M.V.	Mono. R-3 M.V.	Diph. M.V. 1∓	Mono. R-4 M.V.	No defl.	Mono. R-3 M.V.	Mono. R-5 M.V.	Mono. R-10 M.V.	No defl.	Diph. R-8 M.V.	Mono. M.V. 3
QRS-IV		Diph. M.V. 3					Diph. M.V. 10		Diph. M.V. 12	Diph. M.V. 11	Diph. M.V. 7
Q-wave	None	None	None	None	None	None	None	None	None	None	None

in one or more limb leads in seven. In Lead IV the primary complex was invariably diphasic.

The S-T interval was isoelectric in all limb leads. In Lead IV it was isoelectric, or nearly so, in one; the take-off was slightly high in four.

In one of our subjects T_1 was negative. In three others T_1 was isoelectric. T_2 was isoelectric in two; negative in one and diphasic in one. T_4 was positive in four; in one instance T_4 was negative as in the normal adult. (In Figs. 1 and 2 this difference in potential is shown.) We are unable to account for this variation. It is of some interest that the subject from which the negative T_4 was derived was the oldest fetus of the group and that this fetus had made slight

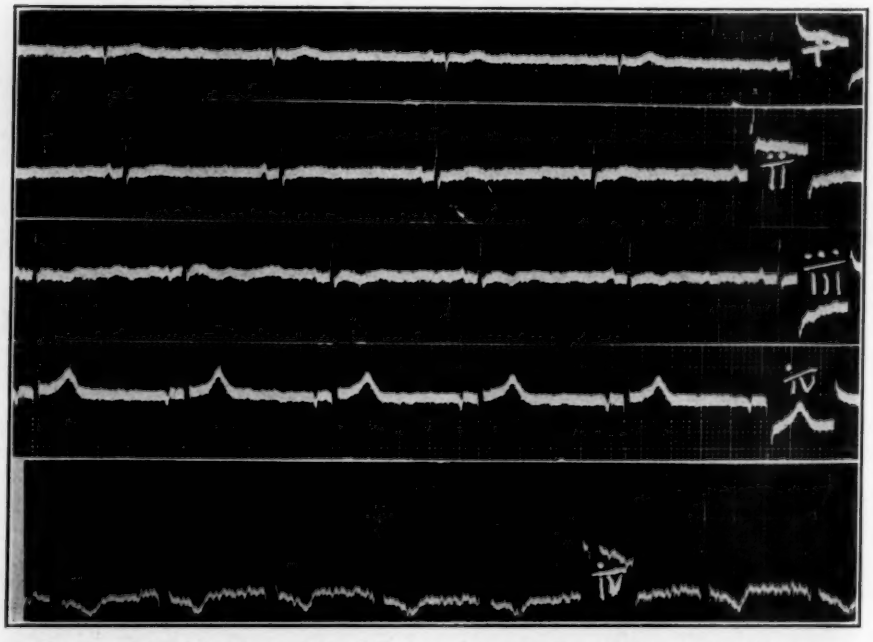

Fig. 1.—Fetus 10 with control adult Lead IV, strip *E*. In strip *D* a positive T_4 is shown, a confirmation which was present in four of the five chest leads obtained (Fetuses 2, 7, 9, and 10).

gasping movements at intervals of one to one and one-half minutes. Of the fetuses from which a positive T had been derived, only one had shown respiratory movements and these occurred at relatively longer intervals. The question arises as to whether a relatively high density of fetal lung may influence the potential of T as derived from anteroposterior chest lead. It is possible that our investigations now in progress may throw further light upon the potential of T_4 as derived from a fetus.

Serial electrocardiograms of the single member of our group in which we were able to continue our observations until deflections

ceased showed the following variations; the progressive slowing noted in the course of all of our serial studies together with periods of asystole, the appearance of a single ectopic beat of ventricular origin, shifting of pacemaker to A-V node, and the gradual widening of the primary ventricular complexes. A similar sequence of events had

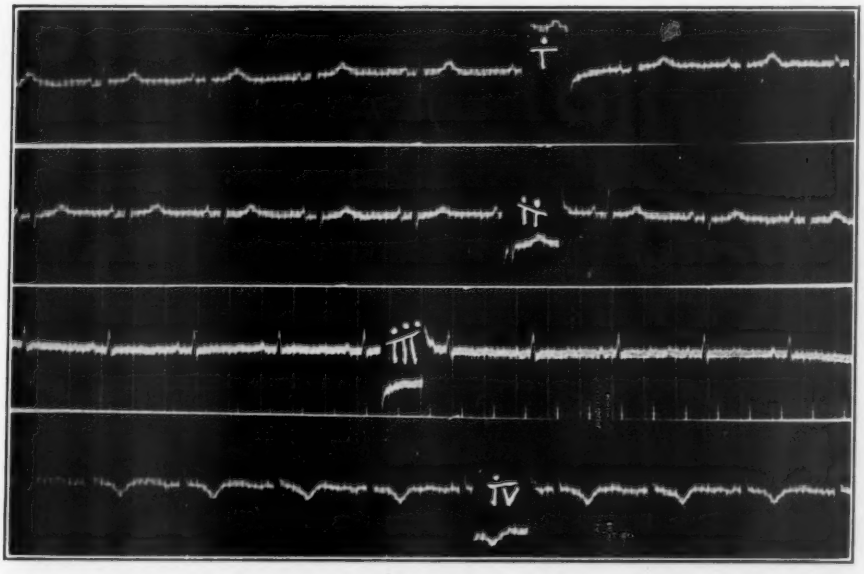

Fig. 2.—In strip *D* is shown the only negative T_4 which occurred in the series (Fetus 11, age estimated at twenty-five weeks).

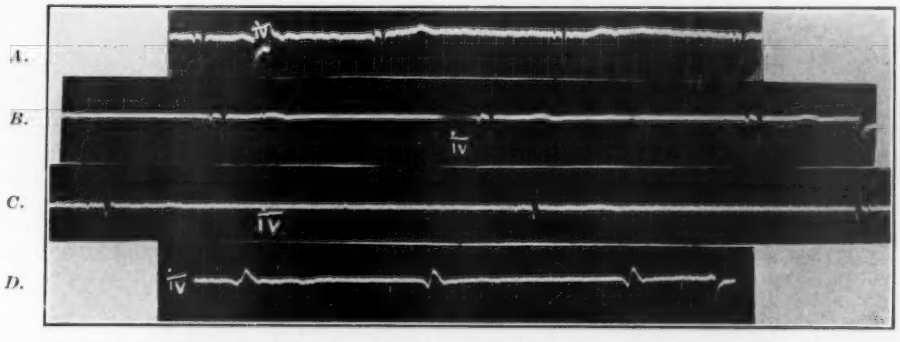

Fig. 3.—Four strips of Lead IV; an interval of about three hours elapsed in securing of records *A* and *D*. The third complex in strip *C* is under dominance A-V node. Strip *D* was secured a few minutes before deflection ceased (Fetus 9, age estimated at eighteen weeks).

been recorded by Hanson, Purks, and Anderson[6] during the course of electrocardiographic studies of the dying hearts of human adults. In their series of twenty-five patients these authors noted that the period elapsing from clinical death to final deflections averages five minutes; the longest period was thirty-five minutes. In their cases

rapid heart action of sinus origin was followed by progressive slowing; the pacemaker was frequently migratory and shifted between the sinus and the A-V nodes; short periods of asystole occurred frequently; heart block and extrasystoles were common; ventricular fibrillation was a frequent terminal event.

Our case adds nothing to the phenomena previously observed in the dying adult heart, except that in our fetuses cardiac activity persisted six times as long as in any of the adult cases of Hanson and his associates. Our series of fetuses is not large enough to permit of generalization, but it would seem probable that, since embryonic tissues are very resistant to asphyxial conditions, activity in dying fetal hearts should persist longer than in the fully developed subject.

CONCLUSIONS

1. Through the use of standard equipment and the employment of the standard technic, satisfactory electrocardiograms may be directly derived from fetuses at very early periods of gestation.
2. In all three limb leads and in standard chest leads, the major deflections which are present in the electrocardiograms of the adult appear.
3. Minor variations from the pattern of the normal electrocardiogram of the adult have appeared in members of our series.

For cooperation in collecting our material and for helpful suggestions as to the analysis of our results, grateful acknowledgment is made to the Obstetrical Staff of the Elizabeth Steel Magee Hospital and to Dr. Davenport Hooker, Dr. C. C. Guthrie, and Dr. A. B. Fuller.

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A STUDY OF LEAD IV OF THE ELECTROCARDIOGRAM IN CHILDREN WITH ESPECIAL REFERENCE TO THE DIRECTION OF EXCURSION OF THE T-WAVE*

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THE chief criteria which have been developed for the normal Lead IV of the electrocardiogram of Wolferth and Wood[1] by these and later investigators[2, 3, 4, 5] are: (1) smoothly rapidly described Q, R, and S deflections, without slurring or notching; (2) a definite Q-wave of over 2 mm. in amplitude; (3) an S-T interval without depression greater than 2 mm.; (4) a T-wave negatively described, with a depth greater than 2 mm.

These criteria hold equally for the anteroposterior placement of the electrodes or for the placement of the first electrode over the second to fourth left sternocostal junctions and the second electrode over the left leg. Some variation in form of the electrocardiogram has been observed by Hoffman and De Long[6] on placement of the respective electrodes in various positions on the anterior and posterior chest walls, but for the standard lead above described no one has reported any striking variations in normal humans from the recognized criteria.

It has been our observation that such variation occurs in at least one characteristic and this fact may warrant some alteration of these standards of normality.

Electrocardiograms were made of fifty normal children who varied in ages from one month to sixteen years. These included the three standard leads, and a fourth lead with the first electrode (right arm lead) over the left second, third, and fourth sternocostal junctions and the second electrode (left arm lead) placed over the sixth to eighth thoracic spines on the posterior chest wall.

In contrast to this series, sixty-six records were selected from the general electrocardiographic files of patients with no proved heart disease and with the standard three leads showing no recognized abnormality other than deviation of the electrical axis.

The summary of the data on these two groups is presented in Table I and Table II. It will be seen that the direction and depth of the P-waves, the QRS complex components, the S-T interval, and the direction and extent of excursion of the T-waves have been entered in Table I; only the T-waves are shown in Table II.

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TABLE I

AN ANALYSIS OF LEAD IV IN 50 NORMAL CHILDREN

NO. OF PATIENTS	AGES IN YR.	AXIS			P				Q AV. DEPTH MM.	R AV. HEIGHT MM.	S			T							S-T		
		RT./NO.	NORM./NO.	LT./NO.	+/NO.	ISO./NO.	DIPH./NO.	−/NO.			NO. ISO.	NO. −	AV. DEPTH MM.	NO. +	AV. HEIGHT MM.	NO. ISO.	NO. DIPH.	AV. DEFLECT.	NO. −	AV. DEPTH	DEPRESSION	AV. DEPTH MM.
10	0-1	5	5	0	1	6	0	3	6.4	6.3	6	4	1	5	1.2	5	0	−	0	−	0	−
10	1-2	7	3	0	1	7	1	1	7.2	5.8	9	1	2	6	2	4	0	−	0	−	0	−
10	2-5	3	6	0	0	4	0	6	8.8	9.8	6	4	2	6	2	4	0	−	0	−	1	1.0
10	5-10	4	5	1	1	2	0	7	8.3	11.8	3	7	4	7	3	4	0	+1−1	0	−	4	1.2
10	10-15	4	4	2	1	2	3	4	7.8	14.2	3	7	3	8	1.5	0	2	−	2	5.5	6	1.2

Analysis of the tables makes it clear that there is one notable difference between the two groups. The electrocardiographic findings in both groups, with one important exception, correspond with the accepted values of normal. This exception consists of a remarkably high incidence of upright T_4-waves in the tracings of the group of children (Table I). The records of thirty-two of these normal children showed frankly upright T_4-waves. There were fourteen records in which an isoelectric T_4 was present, and two in which T_4 was diphasic. Finally, there were only two subjects (aged fourteen and one-half and fifteen years) in this entire group whose records showed an inversion of T_4.

TABLE II

T_4-WAVE FINDINGS IN 66 ADULTS WITHOUT CARDIAC DISEASE AND WITH NORMAL ELECTROCARDIOGRAPHIC FINDINGS IN LEADS I, II, AND III

T_4-WAVE FINDINGS	NO. OF CASES	PERCENTAGE OF TOTAL
Inverted	54 (Average depth 2.7 mm.)	80
Isoelectric	6	9
Diphasic	4 (Average depth 2.8 mm.) (Average height 1.5 mm.)	6
Upright	3 (Average height 1.1 mm.)	5

Among the children's records, there were twenty-three instances of right axis deviation, three instances of left axis deviation, and twenty-three in which the electrical axis was normal. No relationship between the direction of the electrical axis and the direction of excursion of T_4 could be detected. With the exception of the T_4-wave findings, all other measurements of the Lead IV tracings (and of the conventional three leads as well) were within the accepted normal limits.

In contradistinction to the above, examination of Table II, which summarizes the findings in sixty-six adults, shows that in fifty-three of the cases (80.3 per cent) a characteristic "normal" inversion of T_4 was present. In fact, only three of the sixty-six adults showed upright T-waves in Lead IV. Of these three, one was a sixteen-year-old girl who was quite small. The two remaining examples of an upright T_4 consisted of minimal upright deflections, each being less than 1 mm. in height. There were six examples of an isoelectric T_4 and four cases in which the T_4 was diphasic. The diphasic T_4-waves which were encountered averaged 2.8 mm. in downward and only 1.5 mm. in upward excursion. This type of diphasic T-wave in Lead IV is not considered abnormal.[3, 4, 5] Generally speaking, therefore, the findings in our adult cases were quite consistent with the established values of normal.

DISCUSSION

These considerations make it plain that an upright T_4-wave is extremely uncommon in the electrocardiograms of adults without cardiac disease, and confirm the accepted belief that, when present, it constitutes an abnormal finding during adult life in the absence of digitalization.[7] In normal children, on the other hand, an upright T_4 occurs with such regularity that it must be considered to be a normal curve, and in no sense can it be taken to indicate cardiac disease. Diphasic and isoelectric T_4-waves in the electrocardiograms of children are without diagnostic significance and apparently represent transitional forms between positive and negative T_4-waves—neither of which are abnormal in childhood.

SUMMARY

Electrocardiograms were made on a group of fifty normal children, and particular attention was paid to the character of the T-wave in Lead IV. A control group of tracings was made from sixty-six adults who had no demonstrable heart disease and in whom the electrocardiograms were within normal limits.

Sixty-four per cent of the tracings of the fifty normal children showed an upright T_4-wave; 32 per cent exhibited a diphasic or an isoelectric T_4, and in only 4 per cent of the cases was the T_4 inverted. No relationship between the direction of the electrical axis and that of the T_4-wave was discoverable.

The inverted T_4, normal in adult life, is of rare occurrence in the electrocardiograms of normal children, while the upright excursion of T_4 in the electrocardiogram of a child is a normal phenomenon.

We are indebted to Miss Jane Wasserman for technical assistance.

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THE PHARMACOLOGICAL AND THERAPEUTIC EFFECTS OF CERTAIN CHOLINE COMPOUNDS

Results in the Treatment of Hypertension, Arthritis, Organic Occlusive Vascular Disease, Raynaud's Disease, Scleroderma, and Varicose Ulcers*†

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IT IS our purpose not to review the vast literature covering the choline compounds but rather to discuss certain findings from our own experience, based on three years of study and experimentation with certain choline compounds, and over two thousand treatments, using the technic of iontophoresis, previously described by one of us (Kovacs).[1] Our interest has been concerned chiefly with the improvement of local circulation, and, for that reason, the local induction of the drugs by galvanic current seemed worthy of careful study. That these drugs are readily absorbed by this method has been demonstrated beyond a doubt by the fact that all of the general reactions reported resulting from other methods of administration (e.g., subcutaneous, oral, intravenous) have been duplicated innumerable times under our observation by the use of iontophoresis.

A severe reaction resulting from mecholyl iontophoresis might be characterized by the following: (a) a marked flush extending over the face, chest and upper abdomen; (b) increase in pulse rate; (c) a deeper, slower respiration cycle; (d) a marked drop in blood pressure (which has been so profound on several occasions that it was necessary to terminate the experiment with atropine); (e) marked salivation (in one instance as much as 140 c.c. of saliva was collected in 20 minutes); (f) marked lachrymation; (g) profuse diaphoresis; (h) increased intestinal peristalsis with abdominal griping and occasional immediate defecation; (i) occasional substernal pressure; (j) diuresis, to a varying degree; (k) changes in the electrocardiogram resulting in temporary inversion of the T-waves in one or more leads; (l) slight cyanosis at the tips of the extremities, with a drop in surface temperature, which usually rises above original level in from one to six hours; and (m) immediate cessation of effects following the injection of atropin.

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TABLE I

EFFECT OF CHOLINE COMPOUNDS ON BASAL METABOLIC RATES

The variations in the control readings for a given patient may be in part explained by certain other factors, such as discomfort due to superficial skin ulcers present during several experiments or restless nights preceding several experiments

PATIENT C		PATIENT L		PATIENT R		READINGS DURING IONTOPHORESIS TREATMENT	
I Control	− 5	I Control	−11	I Control	+ 4	*Patient M. D.*	
1% mech. ionto.		1% mech. ionto.		1 hr. later, potato chips and Sanka		I Control	
2 hr. later	− 6	1¼ hr. later	−15	1½ hr. later, doryl (1:2,000) ionto.		Normal saline ionto. 20 M.A., 19 min.	
II Control	− 8	II Control	− 9	2½ hr. later	+ 1	Recording taken during treatment	− 6
200 mg. mech. orally		After restless night		II Control	− 4	Mech. 0.5%	
2 hr. later	−10	III Control	−21	0.1 gm. acetylcholine chloride subcut. 1¾ hr. later.	− 7	20 M.A., 18 min.	
III Control	−10	After restful night		III Control	− 5	Recording taken during treatment	± 0
500 mg. mech. orally		Mech. 1,100 mg. orally (vomited small amount?)		1% mech. ionto.		12.5 min. after current was turned off	− 3
2¼ hr. later	− 7	After 2 hr.	−16	2 hr. later	−11		
IV Control	−10	IV Control	−19	IV Control	−13	*Patient G*	
1,000 mg. mech. orally		0.1 gm. acetylcholine chloride subcut. 1½ hr. later.	−20	1% acetylcholine chloride, ionto.		I Control	+ 8
2½ hr. later	± 0	V Control	−19	2¼ hr. later	− 7	During saline ionto.	+ 5
V Control	−12	Doryl (1:2,000 sol.) ionto.		V Control	− 4	During mecholyl ionto.	+ 8
0.1 gm. acetylcholine chloride subcutaneously		1¼ hr. later	−15	1,000 mg. mech. orally		½ hr. after treatment	+ 5
1¾ hr. later	− 6	PATIENT M		1½ hr. later	− 8	*Patient C*	
VI Control	− 9	I Control	−13	VI Control	−11	I Control	+16
Control—no med.		1% mech. ionto.		1,500 mg. acetylcholine orally		During saline ionto.	+17
3¾ hr. later	− 6	1 hr. later	−12	1½ hr. later	− 7	During mecholyl ionto.	+22
VII Control	− 6	II Control	−15			½ hr. after treatment	+19
1,000 mg. acetylcholine chloride orally		1,000 mg. mech. orally					
2¼ hr. later	− 1	2 hr. later	− 9				
VIII Control	−12						
2,000 mg. acetylcholine chloride orally							
2 hr. later	− 4						
IX Control	−10						
1% acetylcholine chloride, ionto.							
2½ hr. later	− 6						
X Control	−15						
Doryl (1:2,000 sol.) ionto.							
2 hr. later	− 9						

Mech. Ionto. → Mecholyl Iontophoresis

In addition, there is a characteristic local reaction, directly under the site of application of the drug. This consists of (a) a feeling of prickling followed by warmth during the treatment; (b) the appearance of goose-flesh immediately after removal of the positive pole; (c) a local blush of the skin; (d) sweating of the skin, which may continue from six to eight hours; and (e) an elevation in surface temperature during treatment, followed by a drop during profuse sweating (with accompanying evaporation), and a rise above the former level in from one-half to five hours. Similar reactions have been produced using carbaminoyl-cholinchloride (doryl) and ethyl-β-methylcholine chloride (weaker) by iontophoresis.*

It should be noted that this description might well be applied to a severe reaction following the use of a slight overdose (subcutaneously or orally) of any of a number of the choline derivatives (mecholyl, doryl, acetylcholine [weaker], pacyl and others). Such reactions have been discussed in detail by Starr and his coworkers,[2, 3] Page,[4] Abbott[5] and others.

It would seem that the range of individual susceptibility to these drugs, regardless of the method of administration, varies markedly, and also that the same individual at different times may show a difference in reaction. Certain individuals who scarcely reacted to iontophoresis during the first treatments later manifested all of the local and general reactions above described. In our previous work, we used a 1 per cent solution of acetyl-β-methylcholine chloride with 20 to 30 milliamperes of current for 20 to 35 minutes. (For details, see Kovacs' reports.[1, 6]) Today, we are using a 0.5 per cent solution and it is possible to get essentially identical reactions with far higher dilutions.

Last year, we noted a marked rise in the basal metabolic rates in two patients. They were controlled as follows: A normal basal metabolism test was taken, using a Benedict-Roth machine. In one case, a reading of 0 was obtained. Normal saline solution was then used for an iontophoresis treatment. The metabolism showed a rise to plus 4 per cent. Mecholyl solution was next used for the iontophoresis, and another reading was made near the end of the treatment. This time the reading was plus 55 per cent. The second patient showed a similar increase to 31 per cent.

This year, Dr. Cameron Bailey has worked on the problem with us, using a more accurate, open-circuit method of metabolic determination. We have used a group of individuals, with a variety of drugs and methods of administration for each patient, in order to attempt comparative studies. The results clearly show that the basal metabolic rate is not profoundly disturbed by the use of the cholines in

*The choline compounds used in these studies were supplied through the kindness of Merck & Company, Inc.

the dosages and methods indicated. Each experiment was performed on a separate day, and the control was taken under usual basal conditions.

A possible explanation of the high readings obtained in the earlier experiment is that the closed circuit method does not permit expectoration and measures the total oxygen utilized. In order to take care of the saliva, the patient continually swallowed, and probably swallowed large amounts of, O_2. With a tube in the mouth and the nose clipped shut, the act of swallowing is extremely difficult and can be accomplished only with a considerable expenditure of energy and some anxiety, both of which raise the rate of heat production. These sources of error are not present in the open-circuit method. Starr and his coworkers[2] report no rise in four cases studied (two with the Benedict-Roth apparatus) after 200 to 400 mg. of mecholyl has been orally administered, but such a dosage would probably be too small to produce a metabolic increase in view of the fact that 1,000 to 2,000 mg. doses were necessary to produce a generalized reaction. Inasmuch as many of our determinations were made while the patients were experiencing marked general reactions, we must conclude that no consistent change in basal metabolic rate results from the use of the choline compounds in the dosages indicated. The

TABLE II

EFFECTS OF DORYL ON BLOOD PRESSURE

Carbaminoyl-cholinchloride (doryl) (1:2,000 solution) by iontophoresis. Treatment twenty minutes at 20 milliamperes.

EXPERIMENT I	EXPERIMENT II	EXPERIMENT III	EXPERIMENT IV
CONTROL 210	CONTROL 160	CONTROL 168	CONTROL 190
STABILIZED 110	STABILIZED 90	STABILIZED 118	STABILIZED 130
3:05 P.M.—Treatment started	11:15 A.M. 160/ 90	11:50 A.M.—Treatment begun	Treatment, 20 milliamperes, 20 min.
Doryl (1:1,000 sol.) 20 milliamperes	Treatment begun	11:50 A.M. 178/130	10 min. after treatment 154/108
3:09 140/60	11:20 A.M. 150/100	12:00 NOON 182/130	
3:10 135/60	11:23 150/100	12:03 P.M. 172/130	
3:14 110/60	11:25 140/ 90	12:08 172/130	
Severe general symptoms. Treatment stopped	11:30 150/100	12:12 152/110	
	Treatment ended	Treatment stopped	
3:20 140/80	11:35 150/100	12:17 120/108	
3:25 140/80	11:40 150/110		
3:30 140/80	11:45 150/110		
3:45 150/90	11:50 130/110		
4:15 140/90	11:55 120/110		
4:30 140/90	12:05 P.M 150/110		
21 hr. after treatment 148/90	12:15 150/110		
92 hr. after treatment 170/86			

marked increase in glandular activity, which is evidenced by the salivation, sweating, etc., and which reaches the peak of activity during the treatment and decreases sharply when the current is turned off, may explain the slight rises noted when the basal metabolism was taken during the treatment.

That the choline compounds lower the blood pressure has been widely recognized. The severity of this action varies from a negligible effect, with a small dosage of acetylcholine, to a very profound effect, with mecholyl[4] or doryl. By using doryl (1:2,000) iontophoresis, we have been able to produce marked drops in pressure, but, like all other reductions following the use of choline compounds, in our experience, these have been very transient. In not one of the more than two hundred patients who were treated with drugs of this group for varying lengths of time up to two years, have we observed a maintained lowering of either the systolic or the diastolic blood pressures. After taking 1 gm. of acetylcholine each day orally for seven days, one patient's blood pressure had even risen slightly from 160/110 to 168/110, although a drop in pressure followed several of the individual doses.

THERAPEUTIC EFFECTS

Although Hunt and Taveau[7, 8, 9] by 1911 published studies of seventy-nine homologous or analogous compounds and pointed out that some of these, such as acetyl-β-methylcholine (then believed to be the alpha compound), might well have clinical value, but few choline compounds have been thoroughly investigated as to their possible therapeutic effects. Of these, acetylcholine chloride has been the most exhaustively studied, largely as a result of the stimulation of the work of Villaret and Justin-Besancon.[10-19, 20] Its value has been reported in a very wide range of conditions, including hypertension,[21] arteriosclerosis,[21] hemiplegia,[22-24] and cerebral artery spasm,[25] epilepsy,[26, 27, 28] peripheral vascular disease,[29, 30] varicose ulcers,[31] angina pectoris,[32] ophthalmological problems,[33-39] ozena,[40] paralytic ileus,[41, 42] hypochlorhydria and hyperchlorhydria,[43, 44] acrodynia,[45] tuberculous sweats,[14] and many other conditions.

Our experience and the experiences of many other American workers have been somewhat disappointing with the use of this drug. At present we use it only when we desire to obtain some vasodilatation and when, for some reason, we cannot use one of the stronger and more stable choline compounds.

Starr[3] has demonstrated the use of mecholyl in the treatment of paroxysmal tachycardia, and we believe that it has been a favorable influence in a few instances in our experience. He also indicated that it might be useful in certain patients with peripheral vascular disease.

We intend to report briefly our therapeutic results following the use of certain of these drugs:

Arthritis.—Kovacs[1, 6, 46] reported, in a preliminary way during 1934, on the effects of mecholyl iontophoresis in chronic arthritis. While he did not claim that its action was in any way a curative one, he reported an encouraging percentage of cases with improvement, as judged by reduction in pain, swelling, stiffness, and general evidences of inflammation. To date, 117 patients have been treated for from two weeks to two years, with an average of two treatments per week, with the following results: Although a few have returned to a completely normal state during this period, we do not feel that any of these patients have been cured by this treatment. Forty-four of these patients have had osteoarthritis; of these, 31 have reported definite improvement, while 13 have noticed no improvement; 73 of these patients have had rheumatoid arthritis, and, of this group, 50 have claimed improvement and 23 no improvement. In the groups reported improved are those experiencing temporary improvement. Symptomatic improvement is always difficult to estimate; and, when we consider (1) the psychological effect of an elaborafe technical procedure, (2) the fact that certain of these patients relapsed to their former state during treatment, and (3) the fact that only a small group retained their improvement after treatments were stopped, we must revalue these encouraging figures. There were certain individuals in both groups who apparently responded remarkably, but we have frequently seen arthritic patients with sudden remissions, regardless of the therapy used at the time. This, then, must be considered a palliative treatment, useful in chronic arthritis, especially of the rheumatoid type, where other methods of physiotherapy directed at the relief of local conditions frequently fail.

Peripheral Vascular Disease: Arteriosclerosis, Thromboangiitis Obliterans, Emboli.—In our experience, patients suffering from organic occlusion of the major vessels without an appreciable factor of spasm (such as arteriosclerosis, old embolic thrombosis, and thromboangiitis obliterans) have failed to respond satisfactorily to any form of choline compound therapy thus far tried. A few instances in which a factor of spasm was also present, in either the major or collateral circulation, apparently responded with the healing of old ulcerations or with an increased exercise period before claudication.

Raynaud's Disease, Scleroderma, Ulcers.—In contrast, we have had strikingly good results in the treatment of Raynaud's disease. Twelve patients treated throughout last winter reported marked improvement: increased warmth, improved color of hands and feet, and a decrease in frequency and severity of the attacks. Four of these patients had severely painful ulcerations, all of which healed completely. In two instances these ulcers were of more than three months' duration and had been steadily increasing in size. One was

complicated by an advanced degree of scleroderma. All four had been considered as candidates for ganglionectomy.

Six of these patients had complicating scleroderma which involved the hands and, in two instances, was widely distributed over the body. Even in these cases the Raynaud syndrome improved definitely. Five of these patients and one with scleroderma of the hands but without the Raynaud syndrome showed improvement as evidenced by a moderate loosening of their skin, which allowed freer motion. In a study of three cases, the capillaries of the fingers became clearly visible to the point where the blood flow could be seen, whereas before treatment it had been impossible to identify the capillaries definitely. One patient with scleroderma became steadily worse during treatment.

This series was treated with local iontophoresis applied to the hands or feet as indicated. The average number of treatments was three a week, and the number was decreased as the improvement permitted. Practically all of these were ambulatory patients. Our estimation of improvement was based on their reactions during the past winter; such observations would be valueless in the spring or summer months.

Two of this group were males. They were the only users of tobacco but discontinued its use at the onset of treatment.

Varicose and Other Ulcers.—In 1930 Dainow[31] reported the healing of twenty-nine cases of varicose ulcers of a series of thirty, by the use of acetylcholine injections (0.1 gm. daily) in addition to the usual treatment of rest in bed and wet dressings or ointments. No ulcer required longer than six weeks to heal (except the one failure). Of 199 cases previously treated in the same way without acetylcholine, 31 per cent failed to heal and forty-nine of the ulcers which healed required more than six weeks.

Because we believed that the local treatment with iontophoresis, using mecholyl, might be even more effective, we began to use it in the treatment of varicose ulcers in October, 1934. We wish to report preliminary findings herewith.

Conditions of experiment were: (1) only patients who had long-standing ulcers and who had not had varicose vein injections or whose ulcers had not responded to injection treatment were accepted; (2) no patient received injections during the course of the experiment; (3) no patients were hospitalized or made to refrain from their daily duties, which, in some cases, included washing, ironing, and even chopping wood; (4) no other form of treatment was used (plain vaseline was permitted during the first few days of treatment if it made the patient more comfortable); (5) mecholyl iontophoresis, using 0.5 per cent solution for twenty to thirty minutes at 20 milliamperes, was given two to three times a week. Several received daily

treatments at first. For each treatment, the asbestos cloth, saturated in the solution, was applied over the foot and leg as high as the knee, but not covering the ulcerated area, until a firm scab had formed over it; after this, the application was also made directly over the healed area. (The electrodes were never applied over the affected area.)

CASE REPORTS

CASE 1.—S. N., male, aged fifty-five years, suffered from a varicose ulcer of twelve years' duration and had had a great variety of treatments without effect. Examination: Right leg, lower third, showed an inflamed, edematous, indurated area, 9 cm. × 4 cm., in the center of which was a deep, punched-out ulcer, 1.8 cm. × 1.8 cm. Greatly dilated, tortuous veins were noted, extending up above the knee. Mecholyl iontophoresis was given three times weekly. Definite evidence of healing was noted after the fourth treatment. The ulcer was healed after the sixteenth treatment, at which time he was referred for varicose vein injections.

CASE 2.—B. K., female, aged sixty-two years, had varicose ulcers of recurrent duration over a period of thirty-seven years. She had varicose vein injections for two and one-half years, and a vein ligation in 1931 gave transient improvement. Examination: On the inner aspect of the lower third of the right leg was a hand-sized erythematous and indurated lesion; the lower half was boggy with two punched-out ulcers each about 2 cm. in diameter. Ten treatments were given during a period of six weeks, at the conclusion of which the ulcers were healed and the tissues firm, although still pigmented. There was no evidence of return after six months.

CASE 3.—A. M., female, aged twenty-five years, had ulceration of eight years' duration following postpartum phlebitis. This had practically incapacitated the patient for eight years although occasionally the ulcer healed for a short period. She had been bedridden for seven months. Examination: Definite bilateral varicosities with pigmented, scaly, brawny, indurated area covering entire right ankle. Just below external malleolus was a punched-out, deep ulcer, about two and one-half centimeters in diameter. After twenty-one treatments with mecholyl iontophoresis during a period of one month, the ulcer was entirely healed. She was able to do her own housework at the end of the first week.

CASE 4.—M. A., female, aged seventy-five years, had varicose ulcers of twenty years' duration. Examination revealed palm-sized, erythematous, indurated, oozing area on lateral surface of the right ankle in the center of which was a weeping ulcer 4.5 cm. × 5 cm. After thirteen treatments, given during a period of three weeks, the ulcer was completely healed. Treatments were continued for several more weeks to prevent the skin from breaking down. There has been no recurrence in four months.

CASE 5.—Patient U., female, aged sixty-two years, had varicose ulcers of twenty-five years' duration. No response to lotions and salves. Present ulcer, one year. Located on the lower third of the leg, the ulcer was 7 cm. × 5 cm., very deep and surrounded by indurated, brawny tissue. Because of the severity of the condition, we gave this patient daily treatments but kept her ambulatory, nevertheless. The ulcer was healed after the fiftieth treatment. We have continued treatments to prevent breaking down of newly formed skin.

CASE 6.—R. S., female, aged forty-seven years, had a varicose ulcer of seven years' duration, located on lower third of leg. The ulcer was 1 cm. × 2 cm. and surrounded by brawny tissue. The ulcer, although persistent, was not deep, and it was completely healed after five treatments, given on an average of twice a week.

CASE 7.—Patient C., female, aged fifty years, had varicose ulcers of twenty-three years' duration. The entire left leg, from the knee to the ankle, was brawny and indurated with numerous punched-out, scattered ulcers and one large ulcer 11 cm. × 6 cm. After the sixteenth treatment (three a week), all ulcers were healed. Treatments are being continued in an endeavor to get the skin in the best possible condition. Throughout the treatment this patient has continued to wash, iron, chop wood, and do all her usual household work.

CASE 8.—Patient J., female, aged fifty-one years, had a varicose ulcer of seven months' duration. Situated on the lower third of the leg was seen a very deep, punched-out ulcer, 2 cm. in diameter. This was healed in eight treatments.

CASE 9.—C. B., male, aged fifty-eight years, had bilateral varicose ulcers of thirteen months' duration. The ulcers had not healed following a variety of treatments, including x-ray therapy (eleven ¼ unit treatments) and vein injections with quinine urea. Examination showed bilateral ulcers on the lower third of the legs. The right measured 5.7 cm. × 4.6 cm., and the left 7.0 cm. × 4.9 cm. Both ulcers were completely healed after the thirteenth treatment.

TABLE III

THE TREATMENT OF VARICOSE ULCERS WITH ACETYL-β-METHYLCHOLINE IONTOPHORESIS

PATIENT	AGE IN YR.	DURATION OF ULCER (CONTROL PERIOD)	SIZE OF ULCER	NUMBER OF TREATMENTS	RESULT
1. S. N.	55	12 yr.	Induration 9 × 4 cm. Ulcer 1.8 × 1.8 cm.	16	Healed
2. B. K.	62	37 yr. (Rarely healed)	2 ulcers, each 2 cm. diameter	10	Healed
3. A. M.	25	8 yr.	2.5 cm. diameter	21	Healed
4. M. A.	75	20 yr.	4.5 cm. × 5 cm.	13	Healed
5. U.	62	25 yr. total (Present ulcer 1 yr.)	7 cm. × 5 cm.	50	Healed
6. R. S.	47	7 yr.	3 cm. × 4 cm.	15	Healed
7. C.	50	23 yr.	Scattered ulcers, largest 11 cm. × 6 cm.	16	Healed
8. J.	51	7 mo.	2 cm. dimeter	8	Healed
9. C. B.	58	13 mo.	Bilateral— Rt. 5.7 cm. × 4.6 cm Lt. 7.0 cm. × 4.9 cm.	13	Healed

Above are reported nine cases with chronic varicose ulcers, all of which were completely and rapidly healed by the use of iontophoresis, using a 0.5 per cent mecholyl solution. No other treatment was used, and the patients were kept at their normal occupations. Thus far, we have had no failures. We realize that it is preferable to close the veins as part of the treatment, and, where feasible, we have recommended injection therapy at the conclusion of each experiment. If these results can be obtained in a large series, this form of treatment

has a definite place in the therapy of cases which do not heal after injections, of which there were several in our series, and in the cases of those patients to whom it is not desirable to give injections because of the presence of diabetes, phlebitis, or other contraindications. We have also used this method in the treatment of various other types of skin ulcers, such as those at the tips of amputation stumps, ulcers apparently due to cold sensitivity, and ulcers of unknown etiology. The results have been encouraging, but these represent only isolated instances in each condition and, hence, are not reported in detail. It is to be expected that, if the etiological factors are not removed, all ulcers of this type will tend to recur unless treatment is continued.*

DISCUSSION

The unexplored possibilities of the choline compounds, from the viewpoint of the pharmacology and therapeutics, should be the basis of much extensive research during the coming years. While the reactions which result from large doses of these compounds (and which are described as the muscarine, nicotine, and circulatory types) are essentially similar, there is, very evidently, on more careful study, a subtle difference in them. For instance, carbaminoyl-cholinchloride (doryl) appears to act somewhat more intensely on the gastrointestinal system but less intensely on the circulatory system than acetyl-β-methylcholine chloride (mecholyl). On the other hand, the ethyl ether of β-methylcholine chloride, which is known to be more stable[47] but less active[48] than mecholyl in body fluids, appears to be more effective in the production of sweating and salivation but less effective in its action on the circulation if used in equivalent pharmacological dosage subcutaneously. The ethyl ether is decidedly less effectual when given by iontophoresis.

Acetylcholine is also ineffectual when used with iontophoresis, and the reactions to subcutaneous injections in ordinary dosage (100 mg.) are almost negligible. We were able to produce, in certain individuals, typical choline reactions with dosages of 2,000 mg. orally administered.

A bromcholine ester (pacyl), dimethyl-dioxypurin-methan-carbon-acid-trimethyl-bromethyl-ammonium, which is very stable in body fluids, is being widely used abroad and is worthy of careful study. It has the advantage of being effective with small oral dosage (1 to 2 tablespoonfuls of pacyl, each of which represents 0.005 gm. of the compound) and is reported to follow closely the action of mecholyl. We are unable to report on the effectiveness of this compound at this time but mention it as representative of many of the choline com-

*Since the preparation of this report a total of twenty-four cases of varicose ulcers have been treated with similar results. These will be reported in a later paper.

pounds which will of necessity be subjected to careful study in the near future. Some of these may prove to be much more satisfactory than any that are being used at present.

SUMMARY

1. The general reactions produced by large subcutaneous or oral doses of the more active choline compounds can be reproduced by iontophoresis, using the same drugs. In addition, there are certain local manifestations which appear at the site of application.

2. On the basis of our experiments there is no consistent, marked change in the basal metabolic rate resulting from the use of the choline compounds in the dosages indicated.

3. Although it is possible to produce a marked drop in blood pressure by the use of several of these compounds, this is a transient effect. We have not seen a single patient who has maintained a lowered blood pressure from the use of these drugs.

4. Iontophoresis with mecholyl has proved to be a palliative method for the treatment of arthritis.

5. In peripheral vascular disease, where organic occlusion has been the major factor, the choline compounds have not been of marked value.

6. In vascular disease in which spasm is the major factor, the use of the choline compounds, as outlined, has proved helpful.

7. A preliminary report on the successful treatment of long-standing chronic varicose ulcers is presented.

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ARTERIOLAR HYPERTENSION IN THE AMERICAN NEGRO*

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THE apparent increase in the incidence of essential or, better termed, arteriolar hypertension with its associated high mortality and attendant morbidity has furnished the impetus for extensive investigative work pertaining to its etiology and pathogenesis. The contributions from animal experimentation, although few in number, have been significant in that their results have made possible refutation of many of the older theories advanced. Nevertheless, the material accomplishments toward a solution of the problem have been attained principally through clinical research. A product of such study is the discovery of a greater prevalence of essential hypertension in the American negro than in the white race.[1] This racial difference in the incidence of primary hypertension, as will be subsequently developed, appears to be of great significance, particularly in view of the fact that the disease is practically unknown among the native African negroes. It is the purpose of this communication to offer an explanation for the occurrence and high incidence of the disease in the American negro and to point out the inadequacy and impracticability of some of the previously proposed theories as to the etiology of arteriolar hypertension.

CONSIDERATION OF THEORIES

Although the etymological qualification of the term "inheritance" has been grossly neglected, much of the voluminous literature on the subject is singularly dogmatic and concordant in support of the hypothesis that essential hypertension is inherited biologically. Based on inference and indirect evidence only, this opinion has prevailed from the time of Sir Clifford Allbutt,[2] who considered essential hypertension a "common hereditary peril," up until the present when Major[3] promises the eradication of essential hypertension in one generation by statutory prohibition of the intermarriage of hypertensive families. An opportunity of putting this theory to test presents itself in the comparative study of the incidence of essential hypertension in the American negro of our section and his African cousins. The observations and studies of Shattuck[4] in Liberia, Heiman and his associates[5] in Johannesburg, Donnison[6, 7] in East Africa, Taylor[8] of the American Zulu Mission Dispensary, Odaley[9] of the Gold Coast Colony, Dry[10] of Northern Rhodesia, and Wakeford[11] of Southern Rhodesia concur em-

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phatically in the conclusion that essential hypertension is extremely rare and almost unknown among the native negro tribes of Africa. In comparison, as we have pointed out and wish to emphasize, their descendants, after a residence in this country of approximately two hundred years more or less, show an incidence of hypertensive cardiovascular disease two and one-half times greater than that of the native Americans. Objection to a comparison in this regard, on the score that heredity is no longer pure in the American negro, is to be anticipated. When applied to the American negroes as a whole such objection is perhaps justified, but, in the South, where black and white alike abhor the hybrid, interbreeding is at a minimum. The evidence of admixture with the white race in the negroes studied by us is negligible and insufficient to reconcile the disparity in the incidence of essential hypertension in the African and American negroes. Even so, to make the theory of inheritance applicable to the existing facts by attributing the incidence of essential hypertension in the American negro to interbreeding with the white race, it would be necessary to assume that all the subjects of our study were hybrids; and furthermore, inasmuch as the incidence of essential hypertension in the American negro is actually greater than that of the white race, it would be necessary to infringe on the mendelian law to explain the higher incidence of a character in the hybrid than in the parent carrying the character.

The difference in the incidence of essential hypertension in the American and African negroes might be attributed to change of climate for which the findings of Roddis and Cooper[12] may be offered in support. These authors observed the blood pressures of American Naval officers in the tropics to be on an average 11.5 mm. below the level considered normal in the temperate zone. These findings are not sufficiently conclusive to find application here, and they lack confirmation in the work of Foster[13] in his study of the blood pressures of Americans and Europeans in China. In addition, there is no evidence which indicates that contrary circumstances would produce opposite results.

Amblard[14] and others have implicated syphilis, and Barach[15] has incriminated past infections as causative agents of essential hypertension. Syphilis and infectious diseases are notoriously prevalent in the American negro. However, when applied to the white race, the theories of syphilis and infections as causes of essential hypertension appear substantially refuted by the data compiled by Walker and O'Hare,[16] Fishberg,[17] Horine and Weiss,[18] and Schulze, Ochsner, and Brown.[19]

Theories attempting to explain essential hypertension on the basis of malfunction of the kidneys with consequent retention of pressor-acting, protein metabolites come up for consideration here in view of a difference in the dietary of the African and American negroes. The native African negro subsists largely on a vegetarian dietary, whereas the

diet of the American negro is excessively rich in protein foodstuffs. Evidence relative to the effect of excessive protein ingestion on the blood pressures of experimental animals is disconcerting. Nuzum and his coworkers[20] reported a rise in the blood pressures of rabbits fed on a high protein diet, but such effects have been subsequently denied by Newburgh[21] and Anderson[22] in rabbits, and Drummond and his associates[23] and Osborne and his coworkers[24] in rats. Further, as Jackson and Moore[25] have surmised, were the evidence from such experiments decisive in incriminating protein food excess as a cause of hypertension, the clinical application of such facts would be another matter, for the conditions of these experiments are not applicable to man. That an excessive ingestion of protein may be a factor not innocuous is intimated by the classical therapeutic regimen employed in primary hypertension today in which protein foods are curtailed to minimal requirements. The rationale of such a plan of management has little to support it except custom, for clinical investigations are concordant in denying excessive protein intake a rôle in the etiology of essential hypertension. The conclusions of Mosenthal[26, 27] are emphatic and are corroborated by the observations of Thomas[28] in studying the incidence of hypertension and nephritis in the Eskimos. Further confirmation is found in Lieb's report[29] on the physical status of Vilhjalmur Stefansson, the Aretic explorer, who subsisted for nine years on a meat diet exclusively.

The American negro is gluttonous, and many of the race are obese. Stengel[30] and Allbutt[2] considered overeating a cause of hypertension. More recently, Terry[31] has reported on a study of a group of obese women, the majority of whom had hypertension; he also observed that frequently reduction in weight was associated with a concomitant lowering of the blood pressure. Slight reduction in weight, as in many of Terry's cases, effects a temporary reduction in blood pressure in a number of obese individuals with essential hypertension, but dietary restriction in normal and thin individuals without elevated blood pressures is capable of producing a similar effect. Not rarely we have observed in obese individuals with a fulminating type of hypertension a spontaneous reduction in weight accompanied by a rising blood pressure. The incidence of obesity and hypertension in the American negro woman is such that their fortuitous association could be anticipated to be frequent without a cause-effect relationship. The menopause, the innocuousness of which we are not willing to accept, also appears at the age when obesity and hypertension are more likely to be present. Our premise that the association of obesity and hypertension is not one of interdependence is substantiated by the findings of Alvarez and Stanley[32] in a study of the blood pressures in 6,000 prisoners and 400 guards in whom they found obesity to have no relation to hypertension under the age of thirty-seven years. Schulze and his asso-

ciates,[19] in a study of 927 cases of essential hypertension in individuals under the age of forty years, were impressed with the rarity of obesity in this group. Hartman and Ghrist[33] observed in analyzing the blood pressures of obese individuals otherwise normal that with an increase in weight there was an increase in the height of the normal systolic pressure without an associated rise of the diastolic pressure, a finding not comparable with the pressures encountered in essential hypertension in which the diastolic elevation is most characteristic. A careful consideration of the accumulated facts seems to justify the conclusion that, although obesity definitely aggravates a preexisting essential hypertension, there is no direct etiological relationship.

Riesman,[34] Hopkins,[35] and Alvarez and Zimmermann[36] contend that the menopause constitutes an unquestionable etiological factor of hypertension in women and offered in explanation the theory of disturbed endocrine balance initiated by an abnormal ovarian hormonal influence. The incidence of hypertensive cardiovascular disease is one and one-half times greater in the negro female than in the negro male.[1] A further significant fact is that the disease tends to appear decidedly earlier in life in the female than in the male. These facts, along with the great prevalence of castrates occasioned by radical pelvic surgery for fibroid tumors and venereal infections among negro women, warrant careful consideration of the menopause as a possible etiological factor of essential hypertension in negro women. Although Polak and his coworkers[37] and Lehfeldt[38] deny such cause-effect relationships, we have observed that negro women at the menopause, particularly surgical menopause, suffer much from emotional disturbances incident to this climacteric epoch; and, like Culbertson,[39] we find abnormal vacillations of the blood pressures in this group the rule, and established essential hypertension indeed common. As a direct cause of essential hypertension, the menopause leaves much to be explained: when considered, however, as an accessory factor, the effect of the menopause on emotional stability lends itself readily to logical correlation with the elucidation which follows.

Much has been written recently concerning the psychical characteristics of the hypertensive type of individual—the American business man who sacrifices all in his conscientiousness to attain success, worried, overambitious, and tense. To this psychical picture the American negro presents an exact antithesis; he is notorious for his lack of ambition, his indifference toward accomplishments, and his slovenly, carefree, easy-going disposition. Yet the negro is by no means stolid, nor does he have the platonic disposition of the Chinese. He is exceedingly emotional and syntonic, vibrating erratically with the environment. His responses to stimuli supplied by his surroundings are exaggerated and lacking in restraint. These overreactions are evident in all the emotions: in fear he is panicky; in happiness he becomes hilarious; in

love he is erotic; in reverence he is overly pious; and in anger he brandishes a weapon with intent to kill. On the other hand, the native African negro, according to Dry[10] and Wakeford,[11] is indifferent, unemotional, apathetic, and disinterested. Unlike the Mexicans and Chinese in this country, the American negro has attempted to emulate his white brother's modern manner of living—that of "making life a problem rather than an art." Although statutably free, racial prejudice dictates, through custom, specific confines which are not insignificant additions to the intricacies of living like the modern American. These circumstances make syntony and emotional reactive resilience necessary to his life, and it is not improbable that the singular psyche of the American negro has been forced upon him by his environment. This is in accord with the view held by Moschcowitz[40] regarding the psyche of white patients with hypertension. The surroundings of the American negro require of him a responsiveness and perpetually bombard him with emotional stimuli in response to which he is unable to exercise restraint. The emotional instability incident to the menopause aggravates this inability to make a satisfactory adjustment to the environment.

The influence of the theories which embodied the organic explanation for the increase in peripheral resistance in primary hypertension has not as yet been erased. For this, the term hypertension itself is largely to blame in that it implies a static phenomenon. The lability of the blood pressure, first recognized by Gumprecht,[41] emphasized by Mosenthal and Short,[26] and reiterated by Ayman,[42] is the most singular characteristic of essential hypertension and is not sufficiently appreciated. These striking fluctuations of the blood pressure imply a morbid physiology, only the sequelae of which can be anatomical. In the opinion of Kylin[43] this lability of the blood pressure is explainable only on the basis of a vasomotor disturbance, which is in accord with the view of Norris and his associates,[44] who state that the vasomotor mechanism in patients with essential hypertension is sensitized and that hypertension in those instances is simply an exaggeration of a normal physiological blood pressure response. These contentions are substantiated by the findings of Mueller[45] that the diurnal and nocturnal fluctuations in blood pressure in normal individuals and in patients with essential hypertension differ only in degree, and that patients with essential hypertension show extreme reactions to stimuli which in normal persons would cause only mild reactions. That is to say, the blood pressure responses to emotional stimulation in the hypertensive and in the normal individual are qualitatively the same, the difference being only from a quantitative standpoint. That the ordinary and usual incidents of life provide stimuli sufficient to cause marked fluctuations in the blood pressures of patients with essential hypertension has been demonstrated by Brown,[46] O'Hare[47] and Mosenthal and Short.[26]

Erroneously, essential hypertension has been considered a disease of middle life. Alvarez[48] directed attention to the frequent occurrence of abnormal elevations of the blood pressure in college students, and his contention that essential hypertension begins in youth is supported by the findings of Glomset.[49] Schulze and his associates[19] concluded from a study of young persons with essential hypertension that clinically established hypertension under the age of forty is not rare. It remains to be shown that the so-called "emotional hypertension" and early essential hypertension are not one and the same; Ayman[42] admits the extreme difficulty of differentiation. Diehl and Hesdorffer[50] have recently shown from a five- to ten-year follow-up study that individuals with intermittent or transient elevation of blood pressure during college years are more likely to have an elevated blood pressure after a period of from five to ten years than are individuals who show no emotional vacillations. That the vasomotor system is sensitized, perhaps in youth, by environmental influences much as reflexes in the central nervous system are capable of being conditioned by environment, is not unreasonable to consider. Reacting repeatedly to environmental stimuli by generalized arteriolar spasm, the arteriolar mesial musculature hypertrophies, thereby further enhancing the paroxysmal blood pressure elevations. Later, as a result of the trauma to the arterioles incident to the abnormal blood pressure excursions, arteriolosclerosis results. Herrick,[51] Ayman,[42] and Schulze and his coworkers[19] have demonstrated that the lability of the blood pressure in patients with essential hypertension varies inversely with the degree of arteriolosclerosis. Thus, as a result of a hyperreactive vasomotor mechanism, the oft-repeated abnormal fluctuations in blood pressure provoked by environmental stimuli may be perpetuated, and persistent abnormal elevation of the blood pressure results. The blood pressure elevation is at first intermittent, later perhaps only remittent, and finally, with the advent of organic changes in the blood vessels incident to the trauma inflicted by the excessive blood pressure fluctuations, the blood pressure elevation is perpetuated. The limits of the present-day definition of essential hypertension includes only a late stage of what is, in all probability, a sequence of related events of common origin. The importance of the recognition of abnormal fluctuations in blood pressure as an early stage of essential hypertension becomes apparent, and the value of lability of the blood pressure as a prognostic aid, stressed by Ayman,[52] becomes obvious. The rate of progress from the initial to the final stage and the amount of damage done to the cardiovascular system by the abnormal fluctuations in blood pressure appear to vary much with different individuals. As in practically all other types of cardiovascular disease, women tolerate the morbid physiology better than men. In the negro, hypertension, like cardiovascular disease of every other cause, takes a fulminating course, more severe in men than in women.[53] Whether the differences in this regard

between races and between sexes, respectively, are the result of a disparity in the material from which the cardiovascular system is made, or of a discrepancy in the amount of exposure to stress and strain, promises long to be a moot question.

It is this concept of the pathogenesis of essential hypertension by which the origin of essential hypertension in the American negro and the discrepancy in the incidence of this disease in the African and American negro, and in the American white race, is most satisfactorily explained at this time. The theory of the inheritance of a dominant character in essential hypertension finds no support here. The inheritance of a predisposition to hypertension can apply only so far as biological equipment to cope with situations is inherited and this would, by and large, be racial. It is the civilization which provides the situations to be met and hence, the exciting factor. Customs and racial prejudices provided by this civilization make the same environment more complex for some races than for others. The negro, biologically unequipped to cope with a complex environment, finds his nervous system subjected to much stress and strain during the process of attempted adaptation to occidental civilization. The vasomotor system, as an integral part of the nervous system, participates in this upheaval and becomes sensitized or conditioned to react with greater agility.

SUMMARY

Attention is directed to the significant fact that, although arteriolar hypertension is practically unknown among the native African negroes, the disease is unusually prevalent in their descendants living in this country, the incidence being actually greater than that in the American white race. The inadequacy of the theory of the biological inheritance of primary hypertension in this connection is stressed. The possible etiological rôles played by climate, diet, infections, and the menopause in the pathogenesis of hypertension in the American negro are discussed. On the basis of the neurogenic concept of the development of hypertension, a theory is elaborated to explain the origin of the disease in the American negro and to account for its high incidence. The importance of the environment as a causative factor is emphasized.

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CLINICAL RESULTS FROM ORAL ADMINISTRATION OF THEVETIN, A CARDIAC GLUCOSIDE*

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THE fruit of yellow oleander, termed the be-still nut in the Hawaiian Islands, yields a glucoside, thevetin, the digitalis-like action of which was first demonstrated by König and Husemann.[1] The exact potency of the crystalline product was recently established by Chen and Chen[2]—the frog minimal systolic dose being between 0.004 and 0.005 mg. per gram and the cat unit 0.85 mg. per kilogram, as compared with the frog minimal systolic dose of 0.0005 to 0.0006 mg. per gram and the cat unit of 0.12 mg. per kilogram for ouabain (G-strophanthin). According to the cat unit, thevetin is therefore approximately one-seventh as toxic as ouabain, weight for weight. Upon the conclusion of the pharmacological work, clinical investigations were undertaken by Arnold, Middleton, and Chen[3] to determine its therapeutic possibilities. It was shown that by intravenous injection the digitalis-like property of thevetin could be readily substantiated. The pulse rate was diminished, compensation restored and maintained, and electrocardiographic changes similar to those caused by digitalis were regularly observed after its administration. No instance of local reaction or thrombosis attended its introduction by the intravenous route.

Our earlier studies[3] included a few cursory observations upon the effects following the oral use of the tincture of defatted kernels and the solution of pure thevetin. By such a method of administration, circulatory improvement seemed obvious, but certain side actions upon the gastrointestinal tract, especially cramps and diarrhea, appeared at the same time, particularly with the tincture. A survey of the literature revealed that such symptoms as nausea, vomiting, and diarrhea were frequently encountered in poisoning cases from be-still nuts and in experimental animals intoxicated by thevetin. Balfour and Maclagen[4] described the occurrence of nausea and a peculiar form of vomiting without distress or retching, but with diarrhea, in two boys who had taken the seeds of *Thevetia neriifolia.* They suggested that "the peculiar vomiting was perhaps an action of the stomach itself, unaided by the abdominal muscles and diaphragm." Descourtilz, cited by König and Husemann,[1] observed nausea as well as shivering and nervous manifestations in a negro who had eaten a kernel of the same plant. The fatal case of be-still nut poisoning

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TABLE

CLINICAL DATA UPON THE RESULTS OF

NO.	AGE	SEX	WT.	PRIOR DIGITALIS	THEVETIN DOSAGE	INTERVAL IN DAYS	STATUS % TOLER.	THERAPY MAINTEN.	INITIAL EFFECT			
									CIRCUL.		GAST.	INTES.
									SUBJ.	OBJ.		
1	73	F	200	0	M. xxv—q.i.d.	4	66	−	+	+	0	0
2	42	M	142	Irregular—1 year	M. viii—t.i.d.	16	−	+	0	+	0	0
3	65	M	118	Irregular infusion	M. viii—t.i.d.	6	−	+	+	+	0	0
4	50	M	142	Maintenance	M. xxv—q.i.d.	4	95	−	0	+	+	+
5	43	M	239	Irregular	M. x—t.i.d.	5	7	−	0	+	0	0
6	57	M	122	Irregular	M. viii—t.i.d.	26	−	+	0	+	0	0
7	74	M	?	Irregular	M. viii—t.i.d.	4	−	+	+	+	0	0
8	65	M	149	?	M. x—t.i.d.	6	13	−	0	0	0	0
9	54	M	108	0	M. xx—t.i.d.	3	45	−	0	+	0	0
									After six days' rest			
10	68	M	180	Maintenance	M. viii—t.i.d.	8	−	+	0	0	0	0
11	55	M	?	Indefinite	M. xv—t.i.d.	3	?	−	0	+	0	0
									Thereafter			
12	67	M	180	0	M. xxv—q.i.d.	3	55	−	0	0	0	+
									After 4 days' rest			
13	64	M	181	0	M. xxv—q.i.d.	3	55	−	+	+	0	0
									After 4 days' rest			
14	63	M	200	Irregular	M. xxv—q.i.d.	4	66	−	+	+	0	0
15	53	M	164	Inadequate	M. xv—q.i.d.	2	20	−	0	+	0	+
									Thereafter			
16	36	M	131	Maintenance	M. viii—q.i.d. M. xv—t.i.d.	4 12	− 94	− −	0 0	0 +	0 +	0 0
17	67	M	122	0	M. xx—t.i.d.	4	55	−	0	0	0	+

*Symbolic value of thevetin therapy:

Circulatory advantage marked, +.

Circulatory advantage less marked and accompanied by minor gastrointestinal effects, ±.

Pronounced gastrointestinal effects and less marked circulatory response, ∓.

Predominant gastrointestinal effects and minor circulatory response, −.

Neither circulatory nor gastrointestinal effect, 0.

Unable to evaluate, ?.

I

THE ORAL ADMINISTRATION OF THEVETIN

FURTHER THEVETIN	SUBSEQUENT EFFECT				COMMENT	SYMBOLIC VALUE OF THERAPY*
	CIRCUL.		GAST.	INTES.		
	SUBJ.	OBJ.				
6 c.c.—1 day	+	+	+	0	Regular control of decompensation; minor nausea with anorexia.	+
0	−	−	−	−	Maintenance without adverse symptoms.	+
Maintenance	+	+	0	0	Unable to tolerate digitalis; no adverse effect—maintenance on thevetin.	+
Maintenance After 3 days' rest	+	+	0	+	Improved tolerance after rest; slight diarrhea after 11 days.	+
0	−	−	−	−	Maintenance without adverse symptoms.	+
0	−	−	−	−	Unable to tolerate digitalis; no adverse effect—maintenance on thevetin.	+
M. viii—t.i.d. 9 days	+	+	0	+	Diarrhea on 13th day.	±
0	−	−	−	−	No circulatory improvement nor adverse effect.	0
M. xx—t.i.d. 2 days	+	+	0	+	After slight diarrhea and then a rest, no adverse reaction on excessive doses of thevetin.	+
M. xx—t.i.d. 16 days	+	+	0	0		
0	−	−	−	−	No circulatory improvement nor adverse effect.	0
M. xv—t.i.d. 12 days	+	+	0	0	Regular control of decompensation. Advantage maintained; no adverse symptoms.	+
M. viii—t.i.d. 16 days	+	+	0	0		
M. xxv—q.i.d. 2 days	+	+	+	+	Early diarrhea continued with circulatory improvement; rest did not improve tolerance.	−
M. viii—t.i.d. 1 day	+	+	+	+		+
M. viii—t.i.d. 1 day	+	+	+	+	Improved circulation succeeded by slight anorexia and discomfort; after rest no adverse symptoms.	+
Maintenance	+	+	0	0		−
0	−	−	−	−	Inadequate response; no adverse effect.	?
M. xv—q.i.d. 7 days	+	+	+	+	Early diarrhea, but circulatory equilibrium reestablished before anorexia and nausea; maintenance without adverse effect thereafter.	+
Maintenance	+	+	0	0		−
Maintenance	0	0	0	0	Only adverse effect—slight nausea; not continued on maintenance dosage.	+
M. xx—t.i.d. after 2 days' rest—for 10 days	+	+	+	+	After early diarrhea, thevetin was pushed to therapeutic effect with slight anorexia and occasional loose stools.	− +

TABLE I—

NO.	AGE	SEX	WT.	PRIOR DIGITALIS	THEVETIN DOSAGE	INTERVAL IN DAYS	STATUS % TOLER.	THERAPY MAINTEN.	INITIAL EFFECT			
									CIRCUL.			
									SUBJ.	OBJ.	GAST.	INTES.
18	65	M	122	0	M. xx—t.i.d.	3	41	–	+	+	0	0
									After 3 days' rest			
19	54	M	126	0	M. xv—t.i.d.	4	31	–	–	+	0	0
									Thereafter			
20	57	M	186	Irregular	M. xv—t.i.d.	8	43	–	+	+	0	0
									After 12 days' rest			
21	66	M	145	Inadequate	M. viii—t.i.d.	5	–	+	+	+	0	0
22	50	M	130	0	M. xx—q.i.d.	7	136	–	0	0	0	0
23	45	M	147	?	M. viii—t.i.d.	7	–	+	+	+	0	0
									Thereafter			
24	45	M	147	Recent	M. viii—t.i.d.	4	–	+	+	+	0	0
25	64	M	161	Inadequate	M. xv—t.i.d.	3	18	–	+	+	0	+
									After 2 days' rest			
26	56	M	?	Recent	M. x—t.i.d.	5	?	–	+	+	0	0
									Thereafter			
27	64	M	178	Inadequate	M. xii—t.i.d.	5	14	–	+	+	0	0
									Thereafter			
28	64	M	170	0	M. xxv—q.i.d.	2	39	–	0	+	0	0
29	57	M	145	0	M. xx—t.i.d.	5	57	–	0	+	0	0
30	65	M	199	0	M. x—t.i.d.	5	8	–	0	+	0	0
31	52	M	183	Remote—none recent	M. xv—t.i.d.	8	8	–	+	+	0	0
									After 3 days' rest			
32	70	M	?	Inadequate—recent	M. xx—t.i.d.	2	?	–	0	+	+?	0
									After 9 days' rest			

CONT'D

FURTHER THEVETIN	SUBSEQUENT EFFECT: CIRCUL. SUBJ.	CIRCUL. OBJ.	GAST.	INTES.	COMMENT	SYMBOLIC VALUE OF THERAPY*
M. viii—t.i.d. after 2 days' rest—for 9 days	+	+	0	+?	Early vagal effect; delayed abdominal discomfort and occasional loose stools and cramps.	+
M. viii—t.i.d. 10 days	+	+	0	+		−
M. xv—t.i.d. 2 days	+	+	+	+	Improved circulation succeeded by anorexia, cramps, and diarrhea; maintenance thereafter with disappearance of adverse effects.	+
M. viii—t.i.d. 33 days	+	+	0	0		−
M. viii—t.i.d. 4 days	+	+	0	0	Conduction changes led to discontinuance; no adverse gastrointestinal effect. Later, nausea, vomiting and cramps on maintenance dosage.	−
M. viii—t.i.d. 12 days	+	+	+	+		
M. xv—t.i.d. 7 days	+	+	0	0	Improved circulation without adverse effects.	+
M. viii—t.i.d. 10 days	0	0	0	0	Neither circulatory nor adverse gastrointestinal effect.	0
M. viii—t.i.d. after 5 days' rest—for 16 days	+	+	0	0	Improved circulation without adverse effects.	+
M. xii—t.i.d. 36 days	+	+	?	0	Continued improvement with nausea on second day only.	
M. viii—t.i.d. 13 days	+	+	0	0	Steady circulatory improvement without adverse effect.	+
M. xv—t.i.d. 2 days	+	+	+	+	Early circulatory improvement succeeded by anorexia, nausea and slight diarrhea; after 2 days' rest, no adverse symptoms.	±
Maintenance	+	+	0	0		
M. x—t.i.d. 5 days	+	+	0	0	Early circulatory improvement with later decline; no adverse symptoms.	+
M. viii—t.i.d. 2 days	−	0	0	0		?
M. xii—t.i.d. 6 days	+	+	0	0	Steady circulatory improvement without adverse effect.	+
M. xv—t.i.d. 20 days	+	+	0	0		
0	−	−	−	−	Slight early circulatory improvement; early death.	?
M. xx—t.i.d. 7 days	0	+	+?	0	Slowing of cardiac rate early; transient anorexia and distress on 10th day.	+
0	−	−	−	−	Slowing of cardiac rate; no adverse effects.	+
M. xv—t.i.d. 2 days	+	+	0	+	Early circulatory improvement succeeded by diarrhea.	±
M. x—t.i.d. 2 days						
M. viii—t.i.d. 1 day	+	+	0	0		
M. viii—t.i.d. 15 days	+	+	0	0	Circulatory advantage maintained; diarrhea stopped.	
M. x—t.i.d. 1 day	0	+	0	0	Discontinued by reason of marked vagal effect; nausea questionable. Very slow pulse led to discontinuance.	+

TABLE I—

NO.	AGE	SEX	WT.	PRIOR DIGITALIS	THEVETIN DOSAGE	INTERVAL IN DAYS	STATUS % TOLER.	THERAPY MAINTEN.	INITIAL EFFECT			
									CIRCUL.		GAST.	INTES.
									SUBJ.	OBJ.		
33	55	M	168	?	M. x—t.i.d.	4	8	–	0	+	0	0
34	57	M	150	0	M. xv—t.i.d. M. x—t.i.d.	1 5	18	–	+	+	0	0
35	73	M	153	0	M. xv—t.i.d.	5	34	–	–	+	0	+
									After 3 days' rest			
36	53	M	175	Maintenance	M. viii—t.i.d. with tr. Bella. M. v—t.i.d.	6	?	+	+	+	0	0
37	54	M	?	Recent	M. x—t.i.d.	2	?	–	0	0	0	0
38	61	M	148	0	M. x—t.i.d.	3	7	–	+	+	0	0
39	24	M	145	Inadequate	M. xv—t.i.d.	6	41	–	+	+	0	0
									After 3 days' rest			
40	57	M	259	Recent	M. xv—t.i.d.	3	11	–	–	–	+	+

in a child reported by Arnold[5] showed nausea, vomiting, and diarrhea, but the child succumbed apparently to the cardiac effects of the toxic principle present in these nuts.

Blas[6] gave thevetin to three dogs by mouth in amounts varying from 5 to 50 cg. The large dose, that is 50 cg., induced salivation in twenty minutes, nausea, vomiting, and diarrhea in one-half hour; whereas with the 5 cg. dose vomiting was delayed until one and one-half hours after its administration. A single necropsy in the series of four observations upon three dogs indicated congestion of the stomach and the liver. Blas stated that he detected thevetin in the vomitus and the liver of this animal. Similar gastrointestinal effects were noted by König and Husemann,[1] who, in addition, pointed out the digitalis-like action of thevetin, as mentioned above. By intra-

CONT'D

FURTHER THEVETIN	SUBSEQUENT EFFECT				COMMENT	SYMBOLIC VALUE OF THERAPY*
	CIRCUL.		GAST.	INTES.		
	SUBJ.	OBJ.				
M. x—t.i.d. 2 days	0	0	0	0	Died 6th day. No maintained advantage nor adverse effect.	0
M. x—t.i.d. 6 days	+	+	0	0	Steady circulatory improvement without adverse effect.	+
M. x—t.i.d. 7 days	+	+	+	+	Early improvement in circulation with slight diarrhea; latter subsided on smaller dose to recur with some nausea.	±
M. x—t.i.d. with tr. Bella	+	+	0	0		
M. v—t.i.d. 8 days					Advantage maintained without adverse effect.	
0	−	−	−	−	Marked circulatory improvement without adverse effect. Slow pulse led to discontinuance.	+
0	−	−	−	−	No circulatory improvement nor adverse effect.	0
M. v—t.i.d. 6 days	+	+	0	0	Fibrillation disappeared; no adverse effect.	+
M. x—t.i.d. 3 days	+	+	+	+	Early distinct advantage lost, and discontinued because of nausea, vomiting and diarrhea.	∓
M. viii—t.i.d. 12 days with tr. Bella	+	+	+	+		
M. v—t.i.d. 6 days						
M. x—t.i.d. 4 days						
M. xii—t.i.d. 7 days						
M. xv—t.i.d. with tr. Bella	−	+	+	+	Disproportionate diarrhea and nausea to later slight circulatory advantage.	−
M. v—t.i.d. 2 days						

venous injection in cats, Chopra and Mukerjee[7] reported the stimulation of intestinal movements. They believed that this action was partly dependent upon the peripheral stimulation of the vagus, for the effect disappeared to a great extent upon the administration of atropine, and partly dependent upon the stimulation of smooth muscles. Stimulation of isolated rabbit's intestines was also observed by Chen and Chen.[2] In their work the minimal emetic dose was determined in both pigeons and cats. When compared with ouabain in cats, thevetin is one-fifth as emetic but one-seventh as toxic, gram for gram. The sigificance of these figures will be discussed in a later section.

The purpose of the present investigation is to ascertain, by oral administration of the solution of thevetin, the efficacy in cases of

cardiac decompensation and to record the frequency of untoward effects. The solution was so standardized that each cubic centimeter was equivalent to 1 cat unit. In most instances, it contained from 20 to 25 per cent alcohol.

RESULTS AND DISCUSSION

The results from the administration of the solution of thevetin to forty patients with varying degrees of circulatory failure are analyzed in Tables I and II. No election of subjects was attempted, and the dosage was calculated in cat units with due consideration for the body weight and the theoretical tolerance as in the case of digitalis formulated by Eggleston.[8] In the more seriously handicapped, this end was sought in not less than four or five days as a rule. The clinical responses, of course, served as the ultimate guide to the thevetin therapy in all cases.

A gross evaluation of the effect of thevetin given by mouth may be gathered from a glance at the column designated "Symbolic Value of Therapy" in Table I. Nineteen patients showed marked circulatory advantage while eight others exhibited less marked circulatory improvement accompanied by minor gastrointestinal effects. In 3 patients (Cases 12, 17, and 39) there were pronounced gastrointestinal effects with less marked circulatory response, and in 2 others (Cases 20 and 40) there appeared predominant gastrointestinal effects with minor circulatory action. The results in 3 individuals (Cases 14, 26, and 28) were suggestive but questionable, and those in 5 additional patients (Cases 8, 10, 22, 33, and 37) showed neither circulatory nor adverse response. In a word, 27 of the 40 patients receiving thevetin by mouth had such circulatory improvements that the use of the drug was deemed definitely justifiable. In 5 patients the gastrointestinal reactions overbalanced the circulatory response so that the therapy of thevetin in them must be considered unsatisfactory. In 8 others neither beneficial nor adverse effects were observed with the doses employed.

The favorable results obtained by the oral administration of thevetin were comparable in all details to those produced by digitalis, or by thevetin intravenously injected.[3] Thus, the slowing of pulse, relief of dyspnea, decrease in venous pressure, increase in vital capacity, diuresis, loss of edema, and typical electrocardiographic changes uniformly occurred. In two instances (Cases 3 and 6), thevetin was successfully substituted for digitalis to which both patients had become intolerant.

An examination of Table II will show that 24 of the 40 cases were practically free from untoward symptoms, while the remaining 16 developed varying degrees of gastrointestinal reactions—cramps and

TABLE II

SUMMARY OF CLINICAL DATA FROM 40 CASES IN TABLE I

CLINICAL OBSERVATIONS		NUMBER OF CASES	CASE NUMBERS
Circulatory Condition	Improvement	32	1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 27, 29, 30, 31, 32, 34, 35, 36, 38, 39, 40.
	Doubtful improvement	3	14, 26, 28
	No response	5	8, 10, 22, 33, 37
Untoward Symptoms	Symptoms absent or so mild as to be negligible	24	1, 2, 3, 5, 6, 8, 10, 11, 14, 16, 21, 22, 23(?), 24, 26, 27, 28, 30, 32(?), 33, 34, 36, 37, 38
	Gastric upset, only (anorexia, nausea, or vomiting)	1	29(?)
	Intestinal disturbance, only (cramps or diarrhea)	5	4, 7, 9, 18, 31
	Both gastric and intestinal manifestations	10	12, 13, 15, 17, 19, 20, 25, 35, 39, 40

diarrhea being more frequent than anorexia, nausea, and vomiting. The side actions of 11 (Cases 4, 7, 9, 13, 15, 18, 19, 25, 29, 31, and 35) of the 16 patients were so mild that the use of thevetin was continued or resumed after a rest. In 4 instances (Cases 12, 15, 17, and 40) the adverse effects preceded any evidence of circulatory improvement, but in others they appeared either simultaneously or some time after decompensation had been brought under control. As with other drugs, there is a great variation in individual susceptibility. For example, a few patients in the present series tolerated 1⅔ cat units of thevetin, four times a day, without any discomfort, while others experienced cramps and diarrhea with ½ cat unit, three times daily. As a whole, however, the larger the dose, the more frequent were the adverse symptoms. The diarrhea and other untoward effects caused by thevetin regularly disappeared within twenty-four to thirty-six hours after its withdrawal. Following a rest period, varying from two to twelve days, 9 individuals (Cases 4, 9, 13, 15, 16, 19, 25, 31, and 35) seemed to tolerate the drug better than at the beginning of the treatment, although in 7 others (Cases 7, 12, 17, 18, 20, 29, and 39) untoward symptoms returned upon the resumption of thevetin. It should be pointed out that a reduction of dosage was made in 8 of the 9 patients who exhibited an increase in tolerance. This leaves only one patient (Case 9), who after a lapse of time could take the initial dose without developing the diarrhea noted at the beginning.

In order to exclude the development of tolerance to thevetin, laboratory experiments were conducted with pigeons, cats, and isolated small intestines of rabbits. It was found that a minimal emetic dose injected by vein and repeated at various intervals (one to four days)

uniformly induced vomiting in both cats and pigeons. Strips of rabbits' small intestines, immersed in Tyrode's solution, contracted to the same height by repeated applications of thevetin, the concentration being 1:125,000. It is obvious that no true tolerance to the glucoside can be demonstrated.

To test the validity of Chopra and Mukerjee's[7] claim that the action of thevetin was partly on the vagal endings of the intestines, three of our patients (Cases 35, 39, 40) were given tincture of belladonna along with thevetin, hoping that the intestinal upsets would be checked. As indicated in Table I, the side actions persisted in two cases in spite of the belladonna therapy. The disappearance of the symptoms in the third one (Case 35) remains a question as to whether it was due to the reduction of dosage or actually due to the desired effect of the belladonna. The results obtained with isolated rabbit's

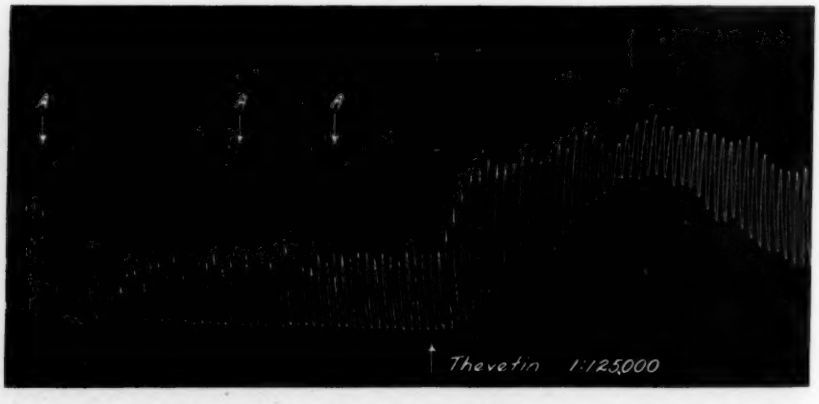

Fig. 1.—Action of thevetin on atropinized intestine.
A strip of the isolated small intestine of a rabbit was immersed in Tyrode's solution maintained at 38°C. At A, atropine sulphate was repeatedly applied until no further response was observed. Without washing, thevetin was added. A prompt response by stimulation resulted.

intestines appear to indicate clearly that atropine does not abolish the thevetin action, as shown in Fig. 1. It seems more logical to employ judiciously dilaudid or morphine to minimize the intestinal reactions, and to keep in mind that the toxic effects of the drug may be masked by such a procedure.[9] This phase of the question is being subjected to further study.

It is possible to formulate an explanation for the relatively more frequent occurrence of gastrointestinal symptoms under thevetin therapy. The mechanism of vomiting caused by digitalis seems to involve a reflex action by way of nerve paths from the heart to the vomiting center in the medulla.[9, 10, 11] The action of digitalis and its allies on the intestines "appears to be a direct one on the muscle itself."[12] Presumably, thevetin has the same modus operandi. With regard to the occurrence of untoward symptoms, even digitalis not

infrequently manifests its toxic effects before its therapeutic advantage is felt. There has been no satisfactory method of obviating the disturbing gastrointestinal action of the digitalis bodies without sacrificing their cardiac effect. It is admitted, however, that with thevetin the occurrence of cramps and diarrhea appears more conspicuous than anorexia, nausea, and vomiting as compared with digitalis. A scrupulous examination of the laboratory data will probably be helpful in elucidating the cause for such differences.

In Table III are listed the results of several crystalline digitalis-like substances, including thevetin, in cats. These figures are se-

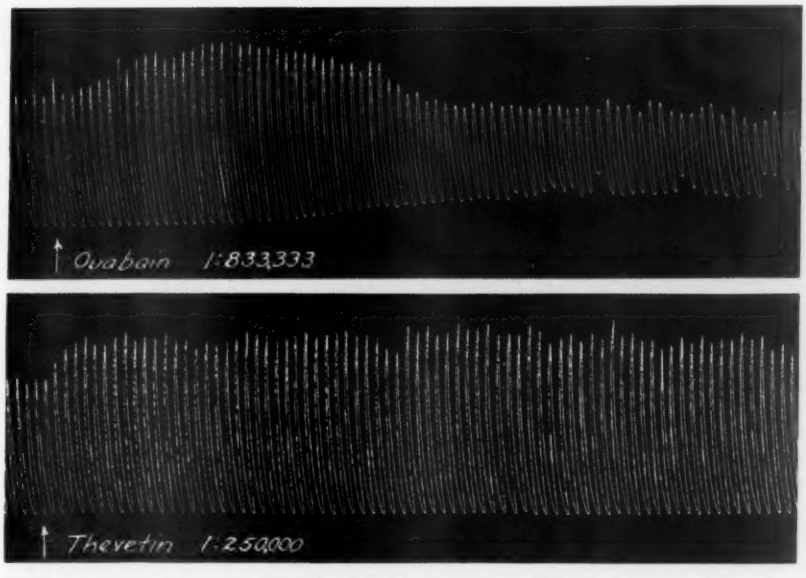

Fig. 2.—Comparison of minimal stimulating concentration of ouabain and thevetin on isolated intestines.

The preparation was similar to that in Fig. 1. The ratio of the concentration of thevetin to that of ouabain is 3⅓:1.

lected from a previous publication.[13] It will be noted that the minimal emetic dose of thevetin is equivalent to 35 per cent of the cat unit, as against 45 per cent for digitoxin and 50 per cent for ouabain. In other words, a physiological unit of thevetin is inherently more apt to cause vomiting than is either digitoxin or ouabain. With the isolated intestines of rabbits, twenty-three out of twenty-nine strips were stimulated by the minimal concentrations of thevetin and ouabain in the ratio of 3⅓:1, as typified in Fig. 2, while the ratio of the cat units between the same is 7:1. This means that the amount of thevetin required to kill the cat is seven times that of ouabain, but the required amount of thevetin to stimulate the intestine is only three and one-third times that of ouabain. A deduction can thus be

made that a physiological unit of thevetin is approximately twice as effective as ouabain in stimulating intestines. These results certainly support our clinical observations upon the relative frequency of gastric and intestinal reactions, particularly the latter.

On the other hand, Table III also shows that it takes a smaller percentage of the cat unit for thevetin to produce early changes of the electrocardiogram in cats, such as P-R prolongation, bradycardia, and ectopic rhythm, than any other substance investigated. Arguing on the same basis as in the case of the gastrointestinal tract, a physiological unit of thevetin would be expected to be approximately twice as effective as ouabain or digitoxin in inducing early signs of digitalization. In the clinical studies, our original intention was to give by mouth the total amount of thevetin of theoretical tolerance within a reasonable period of time, much the same as in the case of digitalis; but it was soon found that circulatory improvement could be attained in the majority of cases with quantities of the drug below the theoretical tolerance, which is a confirmation of our laboratory results. It is not improbable that the incidence of cramps, diarrhea, anorexia, nausea, and vomiting may be further reduced by employing even smaller doses than those recorded in Table I. For example, in a frank case of cardiac decompensation with no previous use of digitalis or similar products, an initial dose of 1 cat unit, three times a day, may be tried. This amount should be increased if digitalization does not become apparent. Similarly, the maintenance dose may be diminished to ⅓ cat unit, three times a day. These suggestions are being put to test, and a separate report will be made at a later date.

TABLE III

COMPARISON OF CAT UNITS: MINIMAL EMETIC DOSES AND ELECTROCARDIOGRAPHIC CHANGES OF SIX CRYSTALLINE CARDIAC PRINCIPLES IN CATS

DRUG	CAT UNIT IN MG. PER KG.	MINIMAL EMETIC DOSE		ELECTROCARDIOGRAPHIC CHANGES IN PER CENT OF CAT UNIT		
		MG. PER KG.	PER CENT OF CAT UNIT	P-R PROLONGATION	MAXIMAL BRADYCARDIA	ECTOPIC RHYTHM
Thevetin	0.85	0.300	35	17	30	31
Cino-bufagin	0.23	0.125	54	18	32	35
Areno-bufotoxin	0.41	0.150	37	37	53	50
Ouabain	0.12	0.060	50	37	58	54
Scillaren A	0.15	0.100	67	46	51	60
Digitoxin	0.33	0.150	45	48	56	61

The results with thevetin bear out certain features which may be particularly interesting to laboratory workers. In the investigation of a new digitalis-like principle or preparation, the mere determination of the cat unit or the frog minimal systolic dose is not sufficient

because it only sets the limit of toxicity. Electrocardiographic studies should give additional information as to its efficacy and promptness in inducing early signs of digitalization. Its emetic index and stimulating action on the intestines should be also qualitatively estimated. To be more specific, it is advisable to make accurate comparisons with ouabain and digitalis (or digitoxin) regarding the following points: (1) cat unit and frog minimal systolic dose, (2) percentage of cat unit to cause early electrocardiographic changes, (3) persistence of action in cats, (4) minimal emetic dose in pigeons and cats, and (5) minimal stimulating concentration to isolated intestines of rabbits. When these data are made available to the clinician, he will be in a better position to recommend proper therapeutic doses.

SUMMARY

1. A series of 40 cases of cardiac decompensation has been treated by the oral administration of thevetin. The results of twenty-seven cases were considered satisfactory because they were parallel to the action of digitalis in all details; those of five were dominated by untoward symptoms; and those of the remaining eight were classified as negative.

2. Thevetin may be advantageously used as a substitute for digitalis in patients who no longer show response or are intolerant to the latter drug.

3. Sixteen of the forty cases showed varying degrees of gastrointestinal effects—cramps and diarrhea being more conspicuous than anorexia, nausea, and vomiting. Of the sixteen, the reactions of eleven were so mild that thevetin therapy could be continued or resumed after a rest.

4. Laboratory data have been supplemented to explain the ease with which intestinal and gastric symptoms occur. Evidence has also been presented to show that by reduction of dosage the side actions may be further minimized without the sacrifice of circulatory response.

5. Attention has been called to the fact that, by more precise evaluation of a new digitalis-like drug, a more accurate estimate of the therapeutic dose may be made. The results of the present investigation indicate that thevetin should be employed in doses of fewer cat units than digitalis.

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FUNCTIONAL BUNDLE-BRANCH BLOCK*

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IN CLINICAL electrocardiography aberrant ventricular complexes of the type recognized as indicative of bundle-branch block have been generally accepted as a sign of diffuse myocardial disease. Recently, however, Wolff, Parkinson and White[1] have called attention to a group of cases, occurring mostly in otherwise healthy young persons subject to paroxysms of tachycardia or of auricular fibrillation, in which the electrocardiograms indicate a bundle-branch block and usually a short P-R interval. In some of the cases reported by these authors, spontaneously or following release of vagal tone by exercise or atropinization, the ventricular complexes have reverted to normal mechanism and the P-R interval has lengthened to be normal. They concluded that aberrant ventricular complexes generally recognized as indicating bundle-branch block may occur in healthy individuals with normal hearts and that the vagus nerve may be responsible for the occurrence of bundle-branch block curves. More recently Wolferth and Wood[2] have reported nine cases of similar nature, in only two of which was there demonstrable organic cardiovascular disease. A reversion of the electrocardiograms to normal could not be produced in any of their cases by exercise or by atropine. They believed that the abnormal mechanism consisted, not of a delay or block, but of an actual acceleration of the passage of the impulse from the auricle to a section of the ventricle. They suggested that the abnormal ventricular complex and the short P-R interval were caused by the passage of the sino-auricular impulse through an accessory auriculoventricular bundle similar to that described by Kent.[3] This bundle was described by Kent as occurring in a certain percentage of mammals and as situated at the right lateral border of the heart. This work, however, does not seem to have been confirmed by other workers, and Lewis[4] has opposed the idea that this abnormal path of conduction ever exists.

Previous to these observations, Wilson,[5] Wedd,[6] and Hamburger[7] reported similar cases. Wilson in 1915 studied his case carefully and stated: "The normal rhythm when spontaneously present could be converted into an atrioventricular rhythm with right bundle-branch block by indirect or direct stimulation of the vagus nerves, and the abnormal rhythm when spontaneously present could be converted into the normal rhythm by the administration of atropine in doses sufficient to paralyze the vagi. This group of facts can lead to but one conclusion,

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and that is the vagi were partially responsible both for the change in the location of the pacemaker and the abnormality of the ventricular complex."

Our interest in this subject was aroused by the observation of two young, otherwise healthy Chinese who were prone to attacks of paroxysmal tachycardia and whose electrocardiograms during the inter-

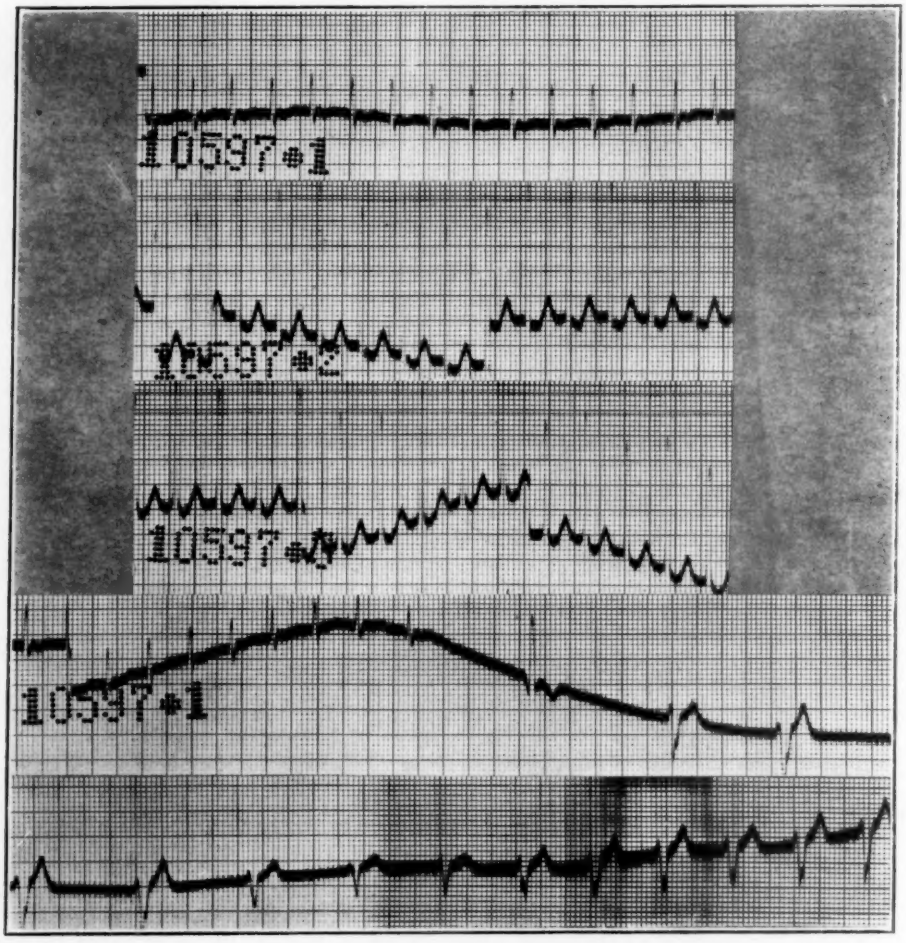

Fig. 1.—Case 1. Leads I, II, and III, above, taken during paroxysmal tachycardia. The third and fourth strips (Lead I) are continuous, showing the transition from tachycardia to bundle-branch block. In these and subsequent curves, each vertical line represents 0.04 second. Unless standardization shows otherwise, each horizontal ruling represents 0.1 millivolt.

val between attacks bore characteristics of bundle-branch block with short P-R intervals. There were three other individuals, not reported in this article, whose electrocardiograms had these characteristics but who did not give a history of paroxysmal tachycardia.

CASE REPORTS

CASE 1.—A healthy staff member of Peiping Union Medical College, aged twenty-nine years in 1932, had been under our observation from Sept. 16, 1929, until Sept. 13, 1934, when he left for a position elsewhere. He first complained of an attack of tachycardia on Feb. 9, 1932. The patient said that he had a similar attack nine years before and once again seven months before. Previous physical examinations and that made on the day after the attack revealed a slightly undernourished but healthy young man. The heart was not enlarged, and there was no significant murmur. Blood pressure was between 106 and 118 mm. Hg systolic and 60 to 70 mm. diastolic. Since then he had had frequent attacks of tachycardia.

A teleradiogram of the heart taken at a distance of two meters on Nov. 8, 1933, showed a heart which was normal in size and shape. Cardiothoracic ratio was 0.45.

Electrocardiograms were frequently obtained and the records during the attack of tachycardia—that showing the transition from tachycardia to bundle-branch

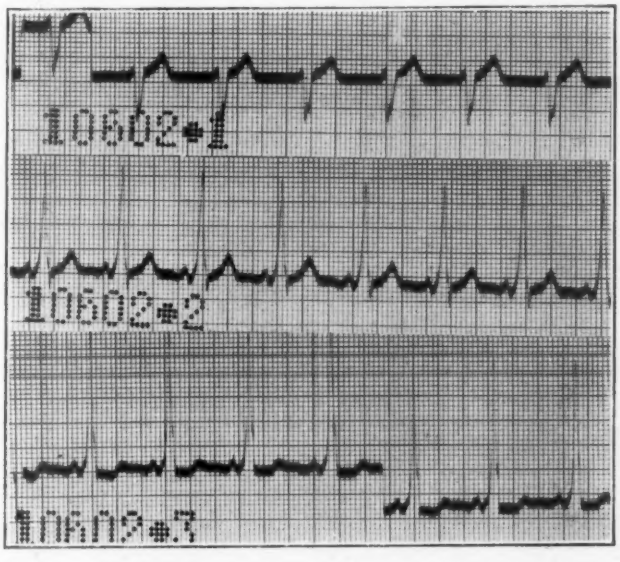

Fig. 2.—Case 1. Leads I, II, and III taken on the next day, showing right bundle-branch block. The curve taken just before the administration of atropine was similar to this.

block and that on the next day—are here reproduced (Figs. 1 and 2). The electrocardiogram in the interval would be generally considered as indicating a right bundle-branch block, with a deep and notched S-wave in Lead I, a widened QRS complex, and a short P-R interval.

On Nov. 9, 1933, two days after a short attack of paroxysmal tachycardia, the subject was given one milligram of atropine sulphate subcutaneously. Electrocardiograms were taken before the atropine, and ten, twenty, and thirty minutes (Figs. 3, 4, and 5) after atropine, and on the next day. There was a gradual, not abrupt, change in the form of the ventricular complex. The P-R interval remained short. The most conspicuous changes consisted, first, in the change of the direction of main initial ventricular deflection in Lead I, from an S-wave to an R-wave, and, second, in the marked shortening of the duration of the initial ventricular complex to normal in all leads. These changes were just as marked twenty minutes as thirty minutes after the administration of atropine. On the next morning a

Fig. 3.

Fig. 4.

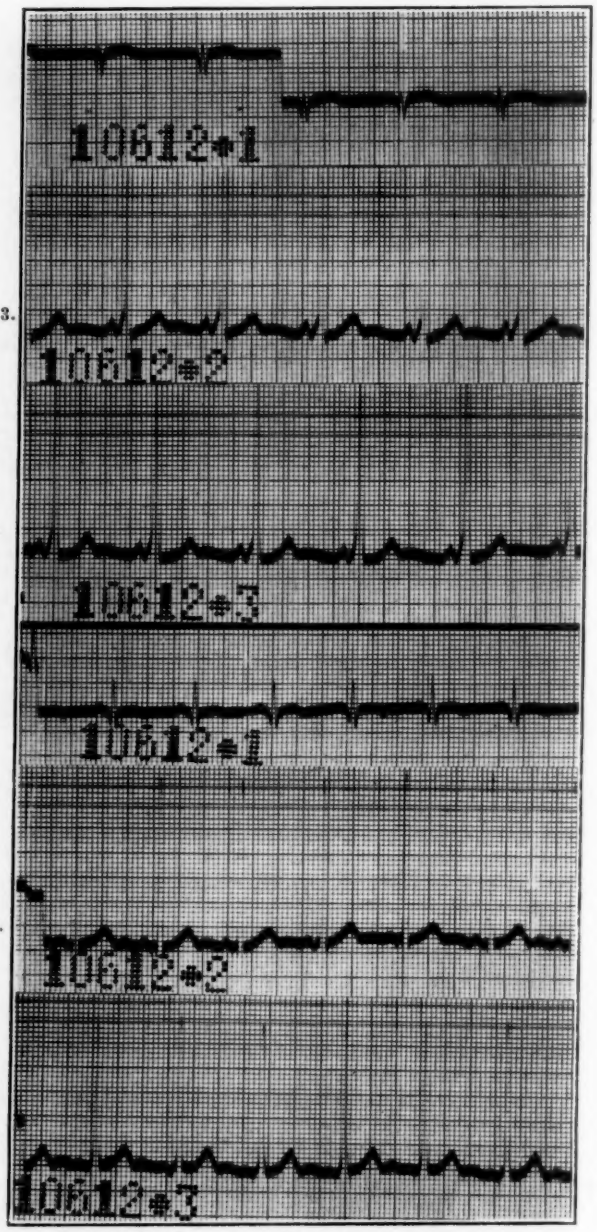

Fig. 3.—Case 1. Leads I, II, and III taken ten minutes after the subcutaneous administration of 1 mg. of atropine sulphate. Note the gradual change of the contour of the ventricular complex.

Fig. 4.—Case 1. Twenty minutes after atropine. Note the normal ventricular complex and normal electric axis.

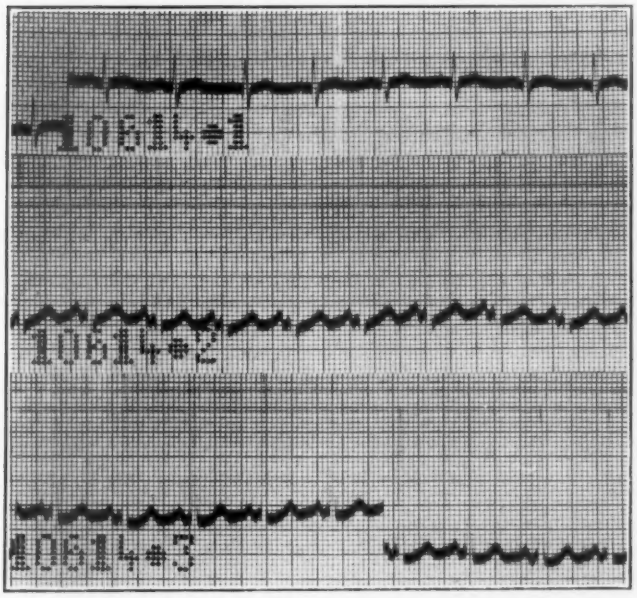

Fig. 5.—Case 1. Thirty minutes after atropine.

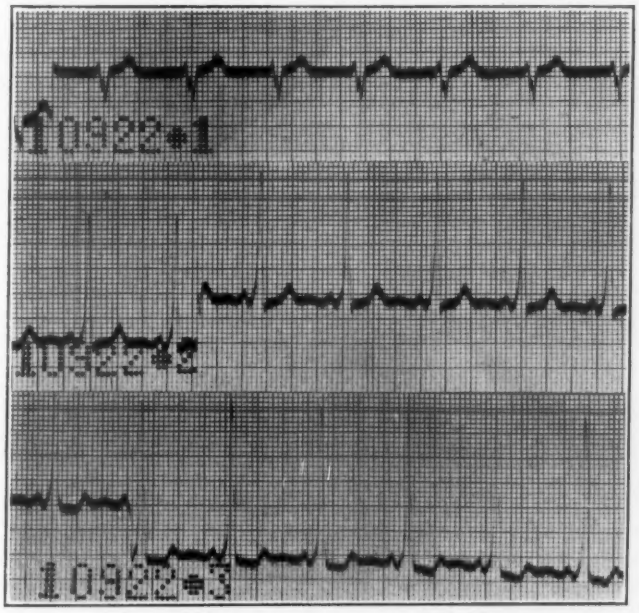

Fig. 6.—Case 1. Leads I, II, and III taken one year later.

reversion of the electrocardiogram to his usual form occurred. Subsequent records were also characteristic of right bundle-branch block curves (Fig. 6).

CASE 2.—A young Chinese male student twenty years old was admitted on March 6, 1934, for repeated attacks of palpitation of heart for eight years. First attack came on at the age of twelve years when the patient was playing, and passed off in a few hours. Sixteen months before admission he developed another

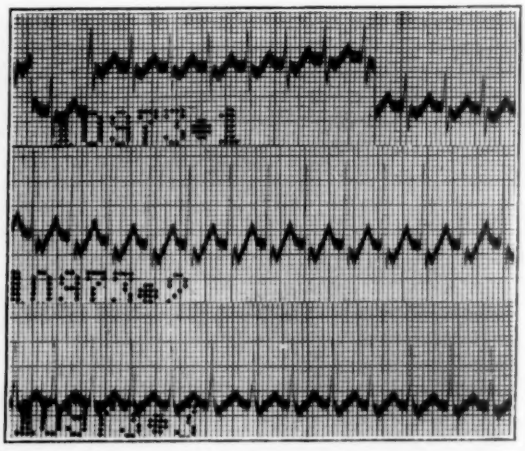

Fig. 7.—Case 2. Leads I, II, and III taken during paroxysmal tachycardia.

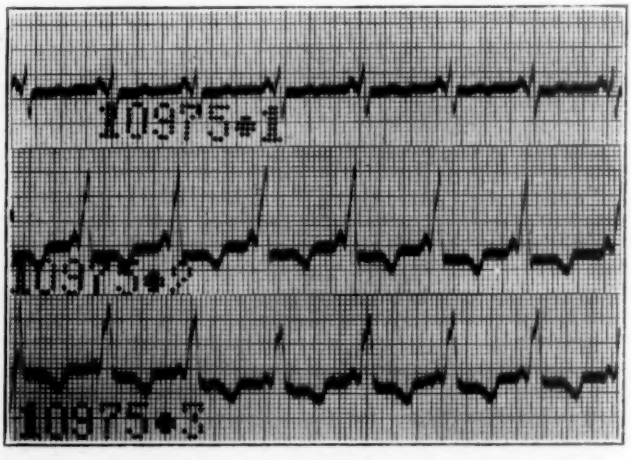

Fig. 8.—Case 2. Leads I, II, and III taken on the next day after cessation of tachycardia.

attack during play; the rapid heart rate was said to have persisted for five days. There were general weakness and some shortness of breath during that attack. The third attack recurred one month after the second. The fourth attack started on the day before admission, when he was climbing stairs. He had been entirely well between attacks. The past history was essentially negative. He was admitted for observation, when the usual methods used in reflex stimulation of the vagus nerve were tried without any effect on the abnormal mechanism.

Examination revealed a healthy young man, in bed, with profuse perspiration on his forehead. The respiratory rate was slightly increased—26 times per minute. There was no venous congestion. The heart was not enlarged. A teleradiogram of the heart showed it to be undersized by 14 per cent according to the method of Hodges and Eyster.[8] The rhythm was regular and the rate rapid, 182 per minute. Radial pulse was small in volume. The attack ceased spontaneously at 3 A.M. on the morning after admission. Laboratory findings were essentially normal. An electrocardiogram was taken on the day of admission (Fig. 7). Several electrocardiograms taken after the cessation of the attack, the last one being taken two months after admission, were similar (Fig. 8). All of them showed short P-R intervals and prolonged QRS durations and low R-waves and short S-waves in Lead I.

On the third day after admission indirect vagal stimulation was attempted. It produced no marked effect on the electrocardiogram until double ocular pressure was employed. This procedure produced a definite change in the form of the R-waves

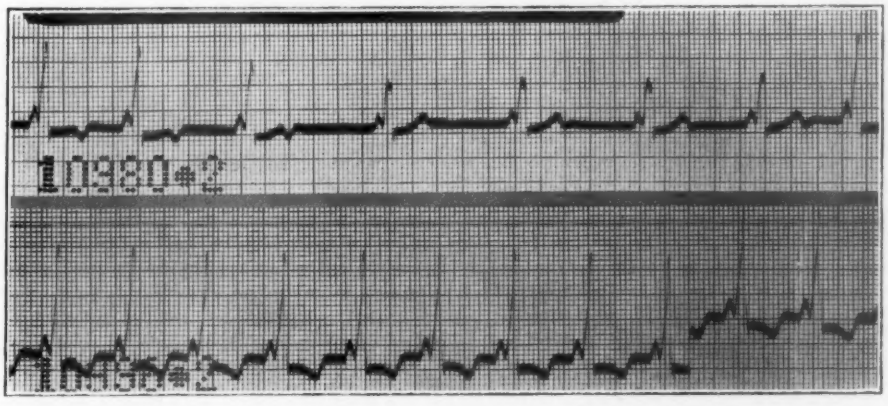

Fig. 9.—Case 2. Upper strip (Lead II) shows the effects of indirect vagal stimulation. The black line represents the time occupied by ocular pressure. The lower strip (Lead II) was taken twenty minutes after the subcutaneous injection of 2 mg. of atropine sulphate.

and T-waves and a slight alteration of the P-wave (Fig. 9). On release of pressure, the complexes reverted to his usual type.

Two milligrams of atropine sulphate were injected subcutaneously. This produced no change in the ventricular complex or in the P-R interval (Fig. 9).

DISCUSSION

These two cases present certain interesting features for discussion. Both of them bear witness to the definite influence of the vagus nerve on the ventricular complexes. In the first subject it appears that the vagus mechanism was at least partially responsible for the abnormalities of the curves since a small dose of atropine (1 mg.) could entirely change the abnormal form of the curves to one which was normal in every respect without even an axis deviation. It is difficult to suppose that a partial release of the vagal tone would deviate the passage of impulse from the hypothetical bundle of Kent, as suggested by Wolferth and Wood, to the usual auriculoventricular conduction path. The only

logical explanation would appear to be that the atropine released the vagal tone which was responsible for the delayed conduction through the right division of the His bundle.

The gradual change in the contour, duration, and axis of the initial ventricular complexes is also against the idea that the auriculoventricular conduction shifted from the accessory to the usual pathway.

Still stronger evidence against the conception of the existence of the right lateral bundle is the significant fact that the curves had the form of a definite right bundle-branch block in the first case and were suggestive of right branch block in the second case instead of a left branch block curve which would be expected if the auricular impulse arrived prematurely at the right ventricular musculature. Stimulation of the right ventricle as shown by direct observation on the exposed human heart[9] always produces an aberrant ventricular complex in which the main initial ventricular deflection is upright in Lead I. Variation in the location of the bundle of Kent or the possible presence of other analogous auriculoventricular connections cannot explain the finding of right axis deviation of QRS in our cases since, even if there be such a path at the left lateral border of the heart, its distance from the sino-auricular node would make it improbable that it could transmit the auricular impulse to the ventricular musculature earlier than through the bundle of His.

In both of these cases, exercise or atropinization did not prolong the P-R interval as it did in some of the cases reported by Wolff, Parkinson, and White. Our findings are not out of harmony with the known action of atropine on the heart.

In the second case it should be remarked that a dose of atropine double that given in the first case produced no alteration in the ventricular complex. Indirect vagal stimulation, however, produced definite changes in both the initial and final ventricular deflections and also a slight change in the P-wave. This constitutes additional evidence that the ventricular complexes in the electrocardiogram of certain individuals can be altered by vagal stimulation.

In regard to the short P-R interval, which was 0.1 second in the first and 0.08 second in the second case, it appears that a rhythm originating in the upper part of auriculoventricular node is a satisfactory explanation. Experimental studies by Eyster and Meek[10] and by Lewis and his associates[11] showed that stimulation of right vagus may cause the pacemaker to migrate from upper to lower portion of the sino-auricular node. Stronger stimulation may produce, in a certain percentage of animals, an auriculoventricular rhythm which, on further stimulation, may migrate from the upper to a lower portion of the auriculoventricular node. Eyster and Meek explained this downward shift of the pacemaker by assuming a gradual diminution in the vagus fibers supplied to the specialized tissue from sino-auricular node downward. Wilson[12] reported three cases in patients in whom an auriculoventricular rhythm

could, at certain times, be produced at will by deep respiration, which he regarded as analogous to vagal stimulation in animals. It is therefore probable that in these cases both the functional bundle-branch block and the short P-R interval are due to an increased vagal tone or an aberrant distribution of the vagus nerves.

The fact that these patients had paroxysmal tachycardia in itself indicates that during the attacks the pacemaker function was assumed by an ectopic focus. This strengthens the belief that in the interval between attacks the pacemaker might also be ectopic and be situated, as suggested, at the upper portion of the auriculoventricular node or its neighborhood. The occurrence of paroxysmal tachycardia has therefore some significance in relation to the shortened auriculoventricular conduction time, but its relation to the abnormal form of the ventricular complexes does not reveal itself.

SUMMARY

Two cases of functional bundle-branch block with short P-R interval occurring in healthy young subjects with normal cardiovascular systems are here reported. Both of the patients were subject to attacks of supraventricular paroxysmal tachycardia.

During attacks of paroxysmal tachycardia the QRS complexes in both cases were entirely normal in form, duration and electrical axis. Upon cessation of the attacks and during the interval between attacks, the electrocardiograms assumed the form of right bundle-branch block.

In one case, upon release of vagal tone by the administration of 1 mg. of atropine sulphate subcutaneously, the electrocardiogram gradually reverted to the normal mechanism with a normal electrical axis. In the other case, while atropinization produced no change in the form of the electrocardiogram, a distinct change in the form of the ventricular complex could be produced by indirect vagal stimulation. In both cases the electrocardiograms during the interval were characteristic of right, not left, bundle-branch block.

It may be concluded that:

a. Aberrant ventricular complexes of the type generally recognized as bundle-branch block may occur in healthy individuals without heart disease.

b. Vagal influence or aberrant distribution of the vagi may be responsible for intraventricular block in healthy subjects. Release of vagal tone may produce a reversion of the abnormal to normal mechanism.

c. Functional bundle-branch block, which is probably of vagal origin, occurs and is not a sign of heart disease.

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HEART FAILURE IN HYPERTENSION*

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THE most frequent cause of death of individuals with essential hypertension is heart failure. It has been estimated by various observers (Romberg,[1] Granger,[2] Murphy and his associates,[3] Bell and Clawson,[4] Scott,[5] G. Fahr[6]) that between 50 and 80 per cent of patients who have sustained essential hypertension develop cardiac insufficiency from which they die. Fahr has calculated that hypertensive heart disease is the most common type of cardiac affection in people over the age of fifty years, and that nearly one-fourth of all deaths in the age group over fifty years are due to this form of heart disease. It is apparent that heart failure resulting from long-continued high blood pressure is a very common and important cause of morbidity and mortality.

There exists no well-defined conception concerning the cause of heart failure in hypertension. Myocardial failure from strain, cardiac muscle fatigue, and similar theories have proved inadequate explanations of circulatory failure in hypertensive subjects.

The present investigation was undertaken to determine whether a study of the post-mortem material from cases of hypertensive heart disease would throw light on the cause of the myocardial insufficiency.

MATERIAL

The clinical histories and post-mortem material of seventy cases of essential hypertension were studied. These seventy cases were divided into two groups. The first series (cardiac group) comprised forty patients with hypertension who presented the clinical picture of heart failure in their last illness. The usual signs of cardiac insufficiency—dyspnea, cyanosis, edema of dependent parts, swelling of the liver, cardiac arrhythmias, and fluid accumulations in the serous cavities, existed in varying combinations and degree. Several instances of sudden cardiac death were included in this group. The second group of cases served as a control. This series was composed of thirty patients with essential hypertension who died as a result of cerebral accidents, renal insufficiency, or coincidental disease, such as carcinoma, etc. None of the cases in this latter group manifested symptoms of heart failure.

The hearts of these seventy patients were studied by gross examination and dissection. Special attention was given to the state of the coronary vessels. In some of these hearts the coronary arterial system was injected with a barium-gelatin mixture after the method of Gross.[7] X-ray films of such injected hearts afforded an excellent

*From the Laboratories and Medical Services of The Mount Sinai Hospital.

method for the study of the coronary vessels (Fig. 1). For microscopic study, blocks were cut from the ventricular myocardium, the interventricular septum, and, in some cases, from the papillary muscles. Sections were stained with hematoxylin eosin and elastica—van Gieson stains.

The hearts from a few of the cases included in this study were no longer available. We are indebted to Dr. Paul Klemperer for the use

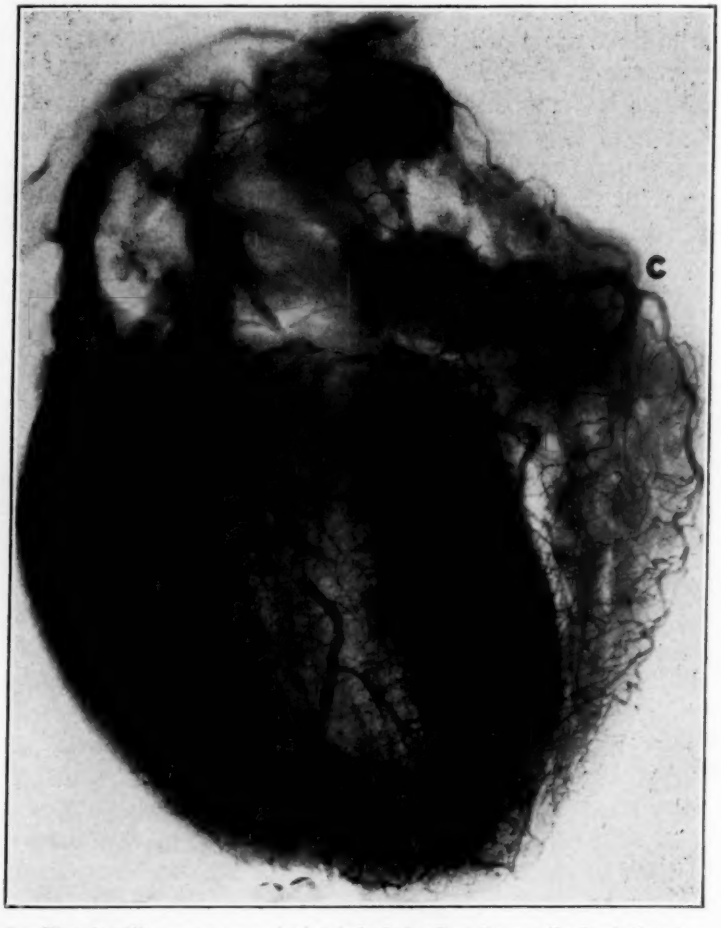

Fig. 1.—Heart with coronary arteries injected after the method of Gross.
A, a break in the left anterior descending artery; *B*, the reduced and irregular lumen of the left circumflex coronary artery; *C*, the comparatively normal right coronary artery.

of the pathological descriptions in such instances. All the patients were from the medical services of Dr. B. S. Oppenheimer and Dr. G. Baehr.

The degree of coronary artery sclerosis is classified in two grades: (a) slight to moderate, and (b) marked. Slight to moderate involvement indicates some thickening of the arterial wall without significant

narrowing of the lumen of the artery. Marked sclerosis implies either localized or widespread pronounced lipocalcific intimal changes with considerably reduced or completely occluded lumen. In addition, careful note was made of the presence of old or recent thromboses in the coronary arteries.

The myocardium was examined grossly and microscopically. Microscopic infarctions, muscle thinnings, aneurysmal dilatations, diffuse fibrosis, and mural thrombi were noted. These changes were also identified in the microscopic study.

FINDINGS

In the cardiac group, 6 of the 40 cases (15 per cent) showed only slight or moderate sclerosis of the coronary arterial system. None of the vessels of these 6 hearts contained thromboses. These cases, which will be discussed later, represent an interesting group of patients with hypertension who die with clinical manifestations of cardiac failure and in whom autopsy fails to reveal sufficient organic cardiac change to account for the heart failure. The remaining 34 cases (85 per cent) had marked coronary sclerosis. In the severely sclerotic vessels of these 34 hearts, there were altogether 31 thromboses. The left anterior descending coronary artery was thrombosed in 13 hearts, the left circumflex in 6, and the right coronary artery in 12 hearts.

In sharp contrast there were only 3 cases (10 per cent) with marked sclerosis of the coronary arteries in the 30 cases of the noncardiac or control group, while the coronary system in the remaining 27 cases (90 per cent) had only slight or moderate sclerosis. None of the vessels in this group of hearts was occluded by either sclerosis or thrombosis. The findings in both groups are summarized in Tables I and II.

TABLE I

DISTRIBUTION OF SCLEROSIS IN CORONARY VESSELS

	LEFT ANTERIOR DESCENDING			LEFT CIRCUMFLEX			RIGHT CORONARY		
	SCLEROSIS		THROMBOSIS	SCLEROSIS		THROMBOSIS	SCLEROSIS		THROMBOSIS
	SLIGHT TO MODERATE	MARKED		SLIGHT TO MODERATE	MARKED		SLIGHT TO MODERATE	MARKED	
Cardiac (40 cases)	8	19	13	9	25	6	7	21	12
Noncardiac (30 cases)	27	3	0	27	3	0	25	5	0

Obvious myocardial scars, aneurysmal thinnings, and dilatations of the muscle and mural thrombi were present in 35 of the 40 hearts in the cardiac group. In the noncardiac group, only 5 of the 30 hearts showed grossly recognizable muscle changes. The other specimens showed hypertrophy of the chamber walls and papillary muscles.

TABLE II

DEGREE OF SCLEROSIS IN CORONARY ARTERIAL SYSTEM

	NUMBER OF CASES	GRADE OF SCLEROSIS	
		SLIGHT TO MODERATE	MARKED
Cardiac	40	6 (15%)	34 (85%)
Noncardiac	30	27 (90%)	3 (10%)

Microscopically, the musculature of the hearts in the cardiac group reflected the severity of the arterial changes. Areas of myocardial necrosis with leucocytic infiltration and large areas of fibrous replacement characterized many of the sections. The muscle fibers were hypertrophied, and there was an increase in the amount of interfascicular fibrosis. It must be noted that, in the six instances in which marked coronary artery changes did not exist, there were nevertheless some myocardial alterations represented by fibrosis and scarring. In the control group of noncardiac cases very marked or severe alterations in the structure of the myocardium were absent. Hypertrophied muscle elements, increase in interfascicular and intrafascicular fibrosis and occasional small patches of fibrotically replaced muscle fibers constituted the essential changes. Large scars, abundant fibrosis, or areas of recent myomalacia did not appear. Neither the type nor the extent of the pathological changes could be considered significant.

Hypertrophy of the left ventricle and, in many cases, of the right ventricle also, existed in the hearts of both groups of cases. This hypertrophy was seen directly in the thickening of the ventricular musculature, the interventricular septum, and papillary muscles. It was further confirmed by an increase in the weight of the hearts.*

In summary it can be said that in the great majority of the hearts of patients who died of hypertensive cardiac insufficiency, there was consistent involvement of the coronary arterial system. The changes in these vessels were marked arteriosclerosis, either generalized or localized, with narrowing of the arterial lumina. Thrombotic or atherosclerotic closure of a main vessel was frequent. Corresponding severe myocardial changes also occurred. In the noncardiac group the coronary system was only slightly affected. Very moderate arteriosclerosis without significant narrowing was the usual change. Coronary artery occlusion from either arteriosclerosis or thrombosis was conspicuous by its absence. Generally the myocardium reflected these minor coronary arterial changes in the relative absence of any pronounced alterations.

DISCUSSION

George Fahr[8] was the first to point out that heart failure unassociated with chronic valvular disease in the great majority of cases (75 per cent) was accompanied by hypertension. Christian[9] observed

*Detailed tables will appear in the reprints of the article.

a systolic pressure of 170 or over in 45 per cent of 400 cases of so-called chronic myocarditis. The validity of the association between elevated blood pressure and heart failure has been definitely established (O'Hare, Calhoun, and Altnow[10]). Strangely enough, no completely satisfactory explanation for the failure of the heart in hypertension has been evolved.

The commonly proposed reason for heart failure in hypertension is final inability of the muscle to work against the increased burden of the heightened blood pressure. There is an impressive array of clinical observation which makes it difficult to accept this simple and seemingly plausible theory that the myocardium of the healthy heart functioning against an increased pressure becomes diseased and fails (Hill).[11] Hypertrophy, which is muscle response to increased work, cannot be considered a pathological state. The efficiency of a heart with hypertrophied nondiseased muscle is not impaired. Lewis[12] points out that in draught and racing horses, and in racing dogs, that is, in animals whose hearts are subjected to long-continued and repeated strains, chronic cardiac maladies are practically unknown. Furthermore, in man, marathon runners and racers do not present a group whose mortality is higher than that of the general population. In a study with the x-ray and the electrocardiograms of 46 rieksha pullers, it was observed that 45 per cent showed definite cardiac enlargement.[13] This cardiac hypertrophy probably was a physiological response to rapid exertion carried on daily for a period of years. There was no indication that the cardiac enlargement constituted or predisposed to heart disease. Coarctation of the arch of the aorta, a congenital malformation which causes a pronounced rise in blood pressure in that portion of the aorta proximal to the narrowing, imposes a strain on the heart which it bears without embarrassment for many years. Patients with this condition die from a variety of causes in the fourth and fifth decades of life. The long duration without cardiac symptoms in coarctation of the aorta, as in cases of essential hypertension, weakens the case for the direct association between increased work and the eventual myocardial failure. It is impossible to rule out the influence of the new factors which might be introduced in the course of years. The effects of infections and toxic agents, or more particularly arteriosclerosis, which invariably is prominent in the later years of life, are of the greatest importance.

Others have reported anatomical changes in the coronary systems and myocardiums of patients who died of hypertension. Most of these workers do not comment specifically upon the occurrence of coronary vessel disease in that group of hypertensive subjects who die of heart failure. Bell and Clawson[4] found that only ten per cent of hypertensive hearts (not only cardiac deaths) were free of coronary arteriosclerosis, that fifty-five per cent were moderately, and thirty-five

per cent severely, affected. From a study of 420 cases of hypertension they conclude that coronary sclerosis is more intense and more frequent in hypertensive than in nonhypertensive cases. Furthermore, they state that two-thirds of all instances of coronary sclerosis are associated with hypertension. S. A. Levine,[14] who analyzed 146 cases of coronary thrombosis, concluded that a previously existing hypertension was probably the most common single etiological factor in the development of coronary thrombosis. Murphy, Grill, Pessin, and Moxon[3] studied 375 patients with hypertension, of whom 188 died of heart failure. They considered this group separately and found that 44, or 25.7 per cent, had gross coronary involvement. They remark, however, that "obviously coronary arteriosclerosis was more common than these figures suggest, but only the cases are included in which the coronary disease was advanced enough to produce definite heart disease and failure." They do not report the incidence of coronary artery lesions in those who died of cerebral vascular accidents, renal insufficiency, or intercurrent disease. Clawson[15] studied the hearts of 115 patients who had hypertension and who died of cardiac failure. Only 12 of these 115 cases, i.e., about 10 per cent, had no coronary sclerosis. In 42.5 per cent of the cases the coronary sclerosis was severe. A. M. Fishberg,[16] who studied the question for many years, writes: "Since I have been following closely the state of the coronary arteries in such patients (hypertensive cardiacs) it has seemed to me that coronary arteriosclerosis is the most common cause of cardiac failure in hypertensive patients." Scott[17] records that more or less coronary arteriosclerosis is almost always found in hypertensive heart failure. Pardee[18] has observed that, if individuals with hypertension develop cardiac symptoms, the clinical picture is similar to that of a patient with coronary artery disease. He is of the opinion that, as long as coronary arteriosclerosis is absent in hypertensive patients, cardiac symptoms will not appear.

From the foregoing it appears that close observers of both hypertensive and cardiac patients agree that the important factor in hypertensive heart failure is coronary arterial involvement. From our analysis herewith presented substantiation of these conceptions is obtained.

Besides the coronary artery sclerosis with narrowing and coronary artery occlusions from arteriosclerosis and thrombosis, pronounced myocardial lesions were found. In the presence of coronary occlusions large infarcts and infarct scars constituted the lesions. In addition, it was noted that there existed diffuse interfascicular and intrafascicular fibrosis to a greater extent than was present in the control group.

It is relevant at this point to discuss the origin of myocardial fibrosis in hypertension. In a paper published in 1924 Clawson[19] says

that it exists only when coronary sclerosis is present and that there is not sufficient evidence to maintain the view that strain causes myocardial fibrosis. In a later publication[15] he states that the myocardium is not severely involved in those cases with coronary sclerosis, although he makes clear that the presence of myofibrosis without coronary artery changes is not uncommon. He concludes that myocardial fibrosis is of slight significance as a cause of heart failure. Victor Levine[20] comes to the same conclusions concerning the frequent lack of correlation between coronary artery sclerosis and myocardial fibrosis. Because of this discrepancy, which he found frequently illustrated in the twenty-seven hypertensive hearts he studied, Levine invokes the theory of a functional disturbance in the fine vascular channels (Ricker).[21] Lisa[22] studied the myocardium of ten cases of decompensated hypertensive hearts. He described areas of granular degeneration with and sometimes without a cellular reaction. Later these cells—usually mixed collections—receded, leaving miliary scars. Other myocardial changes called to his mind the picture of an acute myocarditis. Stains for bacteria and the spirochetes of syphilis were negative. Unfortunately, Lisa did not mention whether or not coronary sclerosis was present. Lisa and Ring[23] studied 100 cases showing myocardial infarction or fibrosis at autopsy. They found 83 per cent of these hearts with moderate to marked coronary arteriosclerosis and 24 per cent with thrombosis of a coronary vessel. Hypertension had existed in 60 per cent of the cases. Madelaine Brown[24] analyzed 110 cases of myocardial fibrosis (chronic fibrous myocarditis) and found disease (thrombosis and sclerosis) of the coronary arteries in 70 of the cases. She advances the suggestion that coronary arterial disease is the most important etiological agent in the causation of myocardial scarring.

In cases in which the myocardial changes result from coronary artery disease, the involvement may be in either the large or small radicles of the coronary system. According to A. M. Fishberg,[25] small vessel involvement occurs in only 3 per cent of cases. This author emphasizes that arteriosclerosis involving the larger vessels is much more frequent in essential hypertension than arteriosclerosis of the smaller arteries. We can confirm the findings of Fishberg respecting the minimal involvement of the smaller vascular elements in hypertensive hearts.

It seems logical to conclude that the widespread myocardial changes which existed in such greater degree in the cardiac group than in the control hearts resulted from the more pronounced artery changes which were found in this group. This correlation readily makes clear the reason for the heart failure in the cases of hypertension which have these changes, for it is acknowledged that coronary artery disease is a factor in heart failure only through its influence on the myocardium.

Although it appears clear from the present study that coronary artery involvement is very frequently found in the hearts of hypertension patients who die with the clinical picture of heart failure and that undoubtedly the heart failure is the result of the coronary artery disease, it is not definitely stated that the hypertensive state stands in any etiological relationship with coronary arteriosclerosis. Nor can one say with absolute certainty whether or not episodes of cardiac breakdown experienced by such patients before the fatal illness were also the result of coronary arteriosclerosis and myocardial insufficiency.[26] However, when one considers the extent of the arterial involvement and the gradual progression of the arteriosclerotic process, it is more than probable that the earlier attacks of heart failure were accounted for by pathological changes similar to those found at autopsy.

Although in the vast majority of cases in the cardiac group sufficient organic changes in the coronary arterial system and myocardium were found to explain the final cardiac failure, there remain the six cases referred to above, in which there were no pronounced macroscopic or microscopic anatomical changes in the heart. Yet these six patients, too, displayed the symptoms of myocardial insufficiency, and death occurred from what appeared to be heart failure.

Chronic pulmonary conditions (bronchitis, emphysema) were present in three of these cases and accounted for the only cardiac symptom, i.e., dyspnea, displayed by the patients throughout life. In each of these cases a severe and rapidly spreading bronchopneumonia ushered in the terminal episode which was characterized by signs and symptoms of cardiac failure, due undoubtedly to the combined effects of the chronic and acute pulmonary conditions. The hypertension played a secondary rôle and actually contributed very little to the production of heart failure. The microscopic examination of the myocardium revealed no significant changes.

The remaining three cases represent a small yet important group* of patients with hypertension who demonstrated the symptoms of heart failure for some time before death. Autopsy did not reveal coronary artery disease of marked degree. Examination of these hearts did not reveal extensive myocardial changes. Although comparatively infrequent, myocardial failure in the absence of acute myocardial damage or coronary artery disease (sclerosis with narrowing, or thrombosis) occurs. It is seen often enough to have stimulated a great deal of speculation and some research. In the earliest treatises on heart failure myocardial insufficiency was considered to be the sole cause for circulatory failure. Romberg,[27] who studied the cardiovascular system in infections, emphasized the myocardial changes. This view was likewise projected by Krehl[28] in a series of publications. Soon it became apparent that frequently there

*Cases of this type will form the basis of a separate publication.

was insufficient anatomical change in the heart muscle to account for heart failure (Aschoff and Tawara[29]). Romberg[27] had suggested that the toxic agents in infectious disease not only affected the myocardium but also had an influence on the peripheral vascular network. This first announcement of the important rôle of the peripheral system in circulatory failure received substantiation in subsequent studies on shock and rapid blood loss (Wenckebach,[30] Kisch[31]). More recent treatises give great prominence to this view (Benjamin,[32] Schottmüller,[33] Blalock[34]).

Eppinger attempted to explain cardiovascular failure in heart disease on the basis of a disturbed peripheral cellular metabolism (Eppinger, Kisch, and Schwarz[35]). Today many believe that the alterations in glycogen and lactic acid metabolism so thoroughly investigated and described by Eppinger and his coworkers *follow* the slowing of the blood stream which accompanies heart failure and that they do not initiate the circulatory insufficiency (Barcroft,[36] Jervell[37]). Once established, these metabolic changes probably complete a vicious cycle and contribute to the circulatory inefficiency. In fact more recently Eppinger himself considered the incomplete resynthesis of lactic acid to glycogen in the peripheral musculature of decompensated cardiacs due to a functional disturbance of the capillary bed. This results from anoxemia which is caused by a slowed blood stream arising from poor heart action (Eppinger, Laszlo, Schürmeyer[38]). The studies of Eppinger have served to give the periphery a renewed and prominent, although not primary, place in the explanation of circulatory failure.

There is again today a definite trend to ascribe heart failure to a primary insufficiency of the myocardium. For instance, Rothschild, Kugel, and Gross[39] have recently shown that in the great majority of cases of chronic rheumatic cardiovalvular disease, myocardial failure is determined by the presence of the active lesions of rheumatic fever in the heart muscle. The mechanical effects of the valvular lesions are well borne into the sixth, seventh, and eighth decades if the muscle is not acutely involved and if other factors such as coronary arteriosclerosis and thrombosis with myocardial degenerations are absent.

Nevertheless, because there are cases such as the three now being discussed which do not present muscle lesions and in which the myocardial changes cannot be ascribed to the effects of infection, or to coronary artery sclerosis and thrombosis, the chemical factors in cardiac muscle physiology have been studied. Kutschera-Aichbergen[40] found a reduction in the phosphatide (lecithin) and calcium content of the heart muscle of patients who died of circulatory failure. Laszlo,[41] T. R. Harrison and his coworkers[42, 43] have also reported lowered phosphate and potassium values in such hearts. The results obtained in animal experiments have confirmed the findings in man. According to these

theories, disturbed chemical balances and irreversible reactions in overworked muscle produce an accumulation of residual metabolites, anoxemia, poor nutrition of the myocardium, and eventual failure. Examination of such hearts at autopsy reveals hypertrophy and dilatation of various chambers dependent upon local circulatory obstructions, but microscopic examination of the heart muscle in some of these cases may not show marked or widespread changes—surely not enough to account for the failure of the heart as an organ. Heart failure here seems to be on a purely functional basis. Much work remains to be done before these chemical explanations of myocardial dysfunction are acceptable.

In attempting to account for failure of hypertensive hearts without pronounced organic changes in the coronary arteries or muscle, great importance has been ascribed to the fact that there really exists a relative insufficiency of the blood supply in these hearts. This is brought about even in the presence of normal coronary arteries by the increased requirements of an hypertrophied heart with greatly increased muscle mass functioning against the added burden of hypertension. The muscle suffers from this slight but long-continued deprivation and eventually fails. Some support for this conception can be derived from a report by Calhoun and his coworkers,[43] who studied the relationship between the thickness of the ventricular muscle fiber, the heart rate, and length of diastole in patients with enlarged hearts. These workers concluded that the slow rate is advantageous to subjects with enlarged hearts "because the recovery period of the heart is prolonged, i.e., it takes oxygen longer to diffuse through a thick fiber than through a thin fiber." They reasoned from this that hypertrophied hearts beating at normal rates may fail from relative anoxemia present under these conditions. It cannot be stated that either unusually low or rapid heart rates occurred in our patients. It is, however, the fact that all had hypertrophy of the left ventricle, and most of the right ventricle, too. The increased muscle mass placed a continued increased demand for oxygen upon the circulation to the heart. Coronary arteriosclerosis with narrowing of the lumen or coronary thrombosis, when it exists, further increases this "circulatory debt."

Severe myocardial changes without sufficient arterial involvement to explain them are relatively uncommon in cases of hypertensive myocardial insufficiency. Likewise, cases of sudden death from heart failure without either a coronary thrombosis or marked myocardial change is unusual. In the series here presented three such instances were encountered. The comparative rarity of such cases emphasizes the fact that most commonly heart failure in hypertension is associated with coronary artery sclerosis and thrombosis and with the effects that such alterations produce in the myocardium.

SUMMARY

In order to investigate the cause of heart failure in hypertension the hearts of forty hypertensive patients who died with symptoms of myocardial insufficiency were studied. As a control group thirty hearts from patients with hypertension who died of cerebral accidents, renal insufficiency, or incidental disease were likewise studied.

Thirty-four (85 per cent) of the cases in the cardiac group had significant coronary arterial involvement (sclerosis or thrombosis), whereas only three (10 per cent) of the cases in the control group had significant coronary artery disease.

The myocardial changes in both groups reflected roughly the extent and degree of coronary artery involvement.

In six (15 per cent) of the forty cardiac cases there was not sufficient organic change in the coronary arteries or myocardium to account for the heart failure. Three of these six patients had marked pulmonary complications. Theories seeking to explain the cause of the heart failure in the remaining three cases are reviewed.

CONCLUSION

Cardiac failure in hypertension is occasioned in the great majority of cases by coronary artery sclerosis and thrombosis which cause degenerative myocardial changes and eventual myocardial insufficiency or sudden death.

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Department of Clinical Reports

TRAUMATIC RUPTURE OF THE RIGHT AURICLE WITH PATIENT SURVIVING NINE WEEKS

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THE history of this case is published for two reasons: first, its extraordinary medical interest, survival for nine weeks after rupture of the right auricle; and second, its unusual medicolegal aspects.

The case came before the Industrial Accident Commission of the State of California on the claim on behalf of the widow that the death was proximately caused by "an accident received in the course of and arising out of employment."

On the basis of the hospital record and the testimony of medical and lay witnesses, two esteemed internists submitted the opinion that the man's illness and death were "nonindustrial," i.e., not due to the alleged trauma but to a diseased condition of the heart. The Commission denied the claim.

Later, Dr. Edwin Merrithew, of Martinez, Calif., who had attended the man, with the attorney for the widow submitted the case to me for my opinion. It seemed that there were a number of features in the clinical history that had not been brought before the examiners or had not been considered by them: first, the normally low blood pressure in the auricle; second, the abnormally low systolic pressure exhibited by the patient; third, the extraordinary strength of the man, his big barrel chest, and his phlegmatic temperament. Moreover, there is quite extensive literature on traumatic rupture of the heart, with some six cases reported in which the patient survived for eight days after rupture of an auricle.

On this review of the clinical history and study of the literature, the Commission reopened the case, and after taking much medical testimony, finally submitted the matter to a panel of three physicians—Dr. Eugene S. Kilgore, Dr. Herbert Allen, and Dr. William Ophüls, all of San Francisco. These gentlemen rendered an unanimous opinion that the injury was the cause of death and that it was "industrial." The Commission then reversed its former decision finding in favor of the widow.

Perhaps the strongest circumstances favoring the opinion were the autopsy findings of a huge hemopericardium, the blood for the most part clotted, an aperture in the wall of the right auricle covered with

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clot, and especially the indisputable x-ray evidence of an immense pericardial shadow which preceded pericardial puncture (Fig. 1) and which persisted.

The following account is largely an abstract of sworn testimony presented at the various hearings, to which some items are added from personal interviews and correspondence.

J. A., aged forty years, a Portuguese dairyman, was a powerful man, 5 feet 5 inches in height, weighing about 200 pounds. His duties were milking and the breaking in of young cattle to be milked by hand and by the milking machine, a hazardous occupation. He was frequently hurt, but being stocky and stout was not much disturbed by being bruised and knocked about. His employer testified that A. worked for him a number of years, in fact up to the time of the accident, often "wrestling with cows. He was awful strong man."

On or about June 24, 1930, while milking a cow, he was kicked in the left lower chest by another cow, was knocked over, and was unconscious for a short time; he

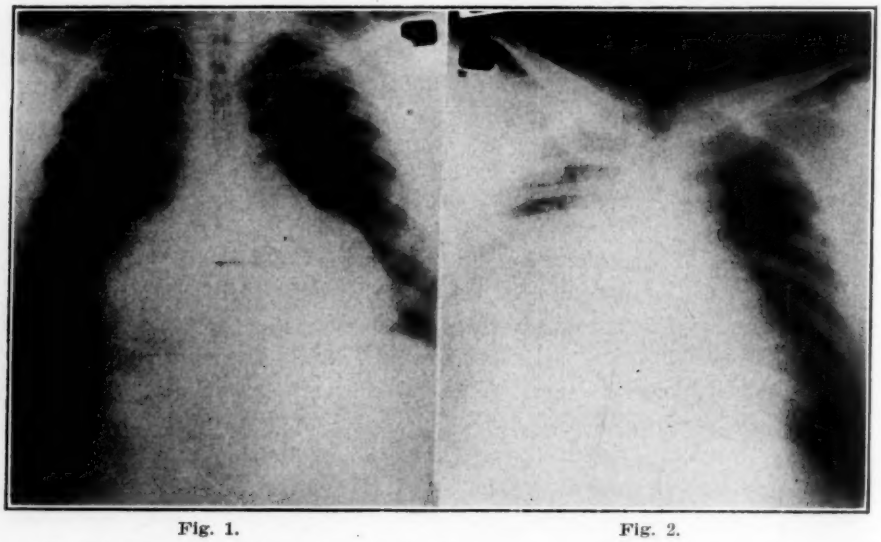

Fig. 1. Fig. 2.

Fig. 1.—Roentgenogram made July 7, 1930.
Fig. 2.—Roentgenogram made July 16, 1930.

was helped to his feet and walked outside the milking shed, but presently (after ten to twenty minutes) returned to his milking. He tried to work for several days after the accident but was very sick, complaining of pain and shortness of breath.

On July 1 he fainted and was carried into the house. This induced him to consult a physician, which he did on July 2, nine days after the accident. Dr. Merrithew said he complained that "he was sick, thought he had 'flu' and couldn't get rid of it." According to the physician, he seemed not to connect his illness with any injury. The doctor described him as a large man who did not look sick. Examination showed "heart sounds muffled, the area of cardiac dullness greatly increased; systolic blood pressure low (90!)." Tentative diagnosis: Myocarditis with dilatation. The patient was advised to go to the hospital, but he objected. A heart tonic, rest and restricted diet were ordered.

On July 7 A. returned to the doctor, unimproved; he was sent to the hospital where his pulse was recorded as 90-96; temperature, 98.6° F.; respiration, 26. X-ray examination showed an enormous pericardial shadow, very dense (Fig. 1). Diagnosis: "Pericardial effusion, probably bloody."

July 10, aspiration of pericardium was performed with large trocar at inner end of left sixth interspace; Dr. Merrithew stating that he removed "a good quart of dark but apparently decomposed blood, which, however, coagulated quickly." Patient did not faint, nor did he show any considerable symptoms of shock from withdrawal of so much blood, nor did the cannula wobble (Merrithew). The blood flow stopped spontaneously. From these facts it seems fair to infer that the blood was not drawn directly from the circulation.

Five hours later x-ray examination showed no perceptible change in the size of the pericardial shadow.

July 11, a second aspiration was performed, about one pint of blood of similar character being evacuated. There was no reaction, but seven hours later the pulse

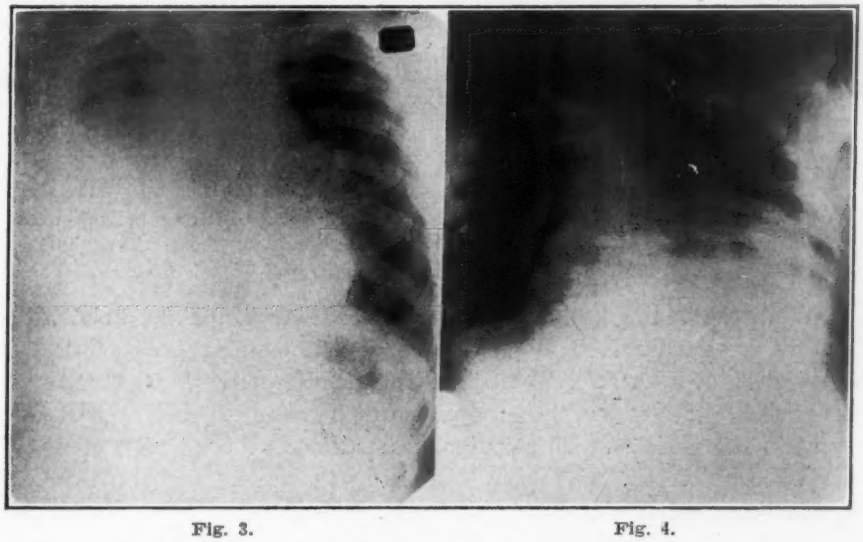

Fig. 3. Fig. 4.

Fig. 3.—Roentgenogram made August 10, 1930.
Fig. 4.—Roentgenogram made December 21, 1929.

became irregular and difficult to count, and patient began to cough. Pulse rate was 102, soon coming down to 90; temperature, 101° F. After ¼ grain of morphine, patient slept practically all night, beginning to cough again in early morning, and then the pulse became irregular.

On July 12 patient became restless and nervous; pulse, 120; temperature, 100-100.6° F.; respiration 30-24; pulse at times irregular; cough troublesome.

On July 16, the x-ray examination showed pericardial shadow considerably larger (Fig. 2) apparently complicated with right pleural effusion, probably inflammatory. With rest in bed, his condition improved; the temperature dropped; the pulse gradually went down to 100 then to 90; respiration, 24-20.

On August 4, x-ray examination showed pericardial and pleural shadows still larger.

On August 5, the third aspiration withdrawing about a pint was performed. Pulse and respiration became quite rapid, the former 100-130; the latter 44-56, with slightly subnormal temperature.

On August 9, there was loss of appetite and considerable precordial pain.

On August 10, x-ray examination revealed: Pericardial shadow still larger with pleural effusion more marked (Fig. 3).

On August 13, patient was well enough to sit up in a chair; pulse, 104-118; respiration, 28-26.

On August 15, he left the hospital against advice, walking. Wassermann reaction was negative.

On August 25, he reentered the hospital; pulse, 130; respiration, 32. Condition progressively worse. Dr. Merrithew judged that operative opening of pericardium was necessary.

On August 26, under ether anesthesia, patient suddenly expired as the skin incision was being made. The chest was not opened.

An autopsy was performed by Dr. Buckmann, local health officer, shortly after death, Dr. Merrithew being present. Permission for the autopsy had been reluctantly given by the widow only on condition that no tissue be removed from the body.

The pericardium was enormously distended with fluid blood and clot, a large part of the clot laminated and adherent to the pericardium and the heart. Dr. Merrithew estimated the amount of clot at the almost unbelievable amount of 5 pounds or more, but the clot was not weighed. After the heart was removed from the body, a thin layer of old clot still adhered to the wall of the right auricle, removal of which exposed a rupture, ½ to ¾ inch long, showing healing at the edges. The heart was not dilated, was about the size of the man's fist and of firm consistency. The valves were normal. There was considerable fat about the ventricles but no evidence of myocarditis. Both coronary arteries were slit open in the examination and found normally patent. There was much fluid in the right chest; the right lung was almost completely collapsed; the other organs were normal.

While the finding at autopsy of an immense laminated blood clot within the pericardium offers an adequate explanation of the failure of aspiration of a quart of blood to lessen the size of the heart shadow, it is probable that after release of pericardial pressure, bleeding from the rent in the auricle which may have ceased was either started up again or was accelerated. For some hours after the second and third aspirations there was restlessness and thirst. After the third tapping, one medical witness testified that the first reaction was relief of dyspnea then "shock, from which however he speedily recovered."

In brief, the argument for the plaintiff was that the deceased was an unusually powerful, hard-working and un-ailing man, stockily built, a stoical individual who had worked at hard labor continuously until the moment of the blow; that thereafter he worked but little, and then with great difficulty; that there was great pericardial effusion at least from the date of the first x-ray plate, July 2, until his death seven weeks later; that aspiration of a quart of blood did not lessen the size of the pericardial shadow; that at autopsy this fact was explained by the amount of solid laminated clot; that a rupture was found in the right auricle, its edges showing evidences of healing; that it was partially sealed over by adherent clot; that six patients in the literature were known to have lived eight days after rupture of an auricle; that rarity did not exclude the possibility of a patient living longer under par-

ticularly favorable circumstances such as obtained in this unusually strong man; that the flow from the auricle was probably slow, even intermittent, because of the normally low pressure in the auricle, the resistance afforded by the clot, and the abnormally low systolic blood pressure (it was only 90 when first recorded, nine days after the accident); that there are in the literature many cases in which rupture of the heart has occurred as a result of blows at a distance, some of them in which the heart was normal.

The argument for the defendant was that the case as claimed was unique; that no one had been known to live more than eight days after rupture of the auricle; that rupture of the heart even if induced by an injury was nearly always due to degeneration of the heart wall, fatty or arteriosclerotic; that the autopsy was not performed by a trained pathologist; that no tissue was removed that could be subjected to expert histological examination; that the heart was probably diseased; that macroscopic examination, even in expert hands, was not sufficient to exclude disease of the wall of the auricle; that men had been known to work with a considerable degree of myocarditis.

Whether one agrees with the claim that the rupture of the auricle occurred on or about June 24, 1930, nine weeks before death, the evidence is uncontrovertible that the man lived seven weeks after the first x-ray plate was taken and the pericardium aspirated. Even on the basis of the only remaining possible hypothesis that the auricle was slit by the trocar on July 10 and the blood withdrawn directly from the auricle, an hypothesis sufficiently negatived above, the survival was still nearly seven weeks.

Being personally greatly interested because it was on my review of the story at the instance of the attending physician that the Commission reopened the case, and not being satisfied as to the condition of the patient's heart before the kick of the cow and learning accidentally that the patient had been in the hospital for a few days some six months previously, I made several trips to the dairy, talked to the man's widow and his employer, and reviewed the record in St. Joseph's Hospital, Stockton, Calif. The employer stated that A. had been in his employ many years; that he had never known him to be ill until December, 1929, nor to have had any serious accident; that during an epidemic of influenza in December he was taken ill with abdominal pain and distention but persisted in working for several days until it was evident that he was seriously sick, when he decided to go to the hospital; that he returned after ten or twelve days and did his regular work for the following six months until kicked by the cow; that in the meantime he seemed perfectly well and worked hard nine or ten hours a day; and that between milking times he was not idle. In reply to questions he stated that patient was not known to have lain down to rest in the daytime, but kept busy, on occasions even hauling water to cattle in the dry pasture, filling the

trough with a bucket from barrels; that his color was always bright, never blue; that he was not short of breath; that his legs did not swell; but that after the kick he was "never good for much."

At St. Joseph's Hospital, Stockton, he was under the care of Dr. L. R. Johnson (since deceased) who left no personal record. The hospital record stated that he entered hospital Dec. 17, 1929. Chief complaint: "Very much gas formation, both in stomach and intestines; some relief after belching; great distention; much pain; no headache; no backache; appetite good but food would not stay down; vomiting; he had been ill for two weeks with stomach trouble; no childhood diseases; severe attack of pneumonia at eighteen years; good recovery; no operations; health very good until present illness." Bedside record showed that the highest temperature was 101° F. on December 19; highest pulse 90; urine, sp. gr., 1.020; negative for albumin and sugar; leucocytes 11,000, 75 per cent polymorphonuclears. Blood pressure not recorded. He was examined by Dr. Jesse Barnes, internist, in consultation, who noted "definite conjunctival icterus, large area of dullness at right base posteriorly nearly to angle of scapula." The hospital report continued: "X-ray film showed marked enlargement of heart to right and left; suspect pericarditis with effusion. Final diagnosis: Influenza. Condition on discharge: Cured."

DENOUEMENT

The above mentioned x-ray plate, taken Dec. 21, 1929 (Fig. 4), is very faint, but it shows a large pericardial shadow difficult to interpret. It is not greatly different from that in Fig. 1, but, since it is evident that the x-ray tube was quite close to the patient, there is some considerable magnification of the heart shadow. It seems almost impossible that the patient could have worked, as testified by his employer, for six months after this plate was taken unless the condition was merely that of big heart, but the shadow may have been due to pericardial effusion, which was Dr. Barnes' diagnosis. At autopsy the heart was apparently of normal size. When these facts were brought to the attention of Dr. Merrithew, he expressed doubt as to the date of the kick by the cow. He said it might have been in December, 1929. The witnesses of the kick of the cow were ignorant Portuguese dairy hands. Was it possible that the employer, being interested in securing the indemnity for the widow, falsified the date of the kick? The records of the Insurance Company showed that the policy was taken out two years before December, 1929, the date of the first illness.

Was the auricle ruptured previous to the December illness, the patient living until the following August—eight months?

Department of Reviews and Abstracts

Selected Abstracts

Harris, I., Jones, E. Wyn, and Aldred, C. N.: Blood pH and Lactic Acid in Different Types of Heart Disease. Quart. J. Med. **16:** 407, 1935.

Under resting conditions lactic acid in the blood is increased in cases of heart failure. The amount of lactic acid stands in a definite relation to the degree of heart failure.

Apart from extreme cases the pH of the blood is normal in different types of heart disease.

The amount of lactic acid formed after a standard exercise stands in a definite relation to the cardiac reserve power. The greater the degree of heart failure the greater the amount of lactic acid formed by standard exercise.

AUTHOR.

Cohn, A. E., and Steele, J. Murray: The Influence of Frequency of Contraction of the Isolated Mammalian Heart Upon the Consumption of Oxygen, Am. J. Physiol. **113:** 654, 1935.

Experiments are described which confirm the observation that the rate at which dogs' hearts beat in heart-lung preparations influences the consumption of oxygen directly. The results reported were observed in two sorts of experiments:

1. In those in which the hearts were driven by induction shocks.
2. In others in which they were not further influenced than by the nature of the preparation itself.

In both methods the change in the rate of consumption of oxygen progressed roughly one-half as fast as change in the rate of contraction. Electrical stimulation itself had no effect on the rate of metabolism.

AUTHOR.

Cohn, A. E., and Steele, J. Murray: The Metabolism of the Isolated Heart of Dogs Related to Age. J. Clin. Investigation **14:** 915, 1935.

Decrease in the consumption of oxygen with age was observed in heart-lung preparations made in pure bred female wire-haired fox terriers of known age living under similar environmental conditions and having been given similar food. Those variable factors in the life of the preparation which could be arranged were controlled; the effects of those which were uncontrollable were calculated. The degree of relationship between age and consumption of oxygen per unit of weight of heart was considerably less when account was taken of certain functions found to be related to both (age and oxygen consumption) but was still significant.

The evidence suggests that, although rate of contraction, size, and, in intact animals, the amount of work done play a part in the decrease of metabolism with age, there is, in addition, a change in structure of the heart or in its composition with age which leads to reduction in the amount of oxygen consumed by each unit of its weight.

A technical observation is believed to be of sufficient importance to deserve mention in the conclusion. When the lungs are exposed to ether even for brief periods, they are likely to become edematous—but apparently not otherwise.

AUTHOR.

Friedman, Ben, Clark, Gurney, Resnik, Harry, Jr., and Harrison, T. R.: Effect of Digitalis on the Cardiac Output of Persons With Congestive Heart Failure, Arch. Int. Med. **56:** 710, 1935.

The effect of digitalis on the cardiac output of patients with congestive heart failure has been investigated by the acetylene method. Prior to the administration of digitalis, most of the subjects had subnormal values from the cardiac output.

Of twenty-two patients, three showed no improvement after the administration of the drug; ten had subjective benefit; and eight exhibited definite objective improvement. In each of the groups some of the patients showed an increase in the cardiac output per minute, some a decrease, and some no change. Consistent alterations of the cardiac output in proportion to the oxygen consumption were not observed.

AUTHOR.

Thompson, W. P., and Levine, S. A.: Systolic Gallop Rhythm: A Clinical Study. New England J. Med. **213:** 1021, 1935.

Thirty-five patients with systolic gallop rhythm observed over a period of eleven years are reported. This number represents 16 per cent of all patients with gallop rhythm encountered during this period.

The extra sound in systolic gallop rhythm is placed in systole between the normal first and second sounds. In most cases it has a quality resembling the normal first sound. Its maximum intensity is usually in the region of the apex of the heart. Its intensity is variable in different patients and occasionally in the same patient from time to time. It may alter its intensity or even disappear with change in the position assumed by the patient, although generally it is loudest in the recumbent position. It may also appear or disappear without apparent cause.

Two-thirds of the group had no cardiovascular disease. Most of them had no complaints, having been seen in consultation because of suspected heart disease, or they presented bizarre complaints of a minor or functional nature. Most of them were "nervous" people. The remainder of the group, twelve in number, had demonstrable cardiovascular disease. Five of them had coronary artery disease, two of these and six others had arterial hypertension, usually mild in degree, and one had bundle-branch block without other evidence of cardiovascular disease. Valve defects, congestive failure or congestive signs of any sort were not found. Only two patients had cardiac enlargement. Significant electrocardiographic abnormalities were absent except in four of those with coronary disease and the one with bundle-branch block. No real incapacitation was present except in those with coronary artery disease.

Extremes of age were eleven and seventy-one years. With one exception in each group, those below forty-four years of age had no cardiovascular disease, and those above forty-four had such disease. Males were predominant in the group with cardiovascular disease, while there was no difference in the number of males and females in those without it.

None of the group is dead at the time of this report while 46 per cent of the group with diastolic gallop observed over the same period are dead. The rarity of cardiac enlargement and physical incapacitation, the slight degree of arterial hypertension in those who had it, and the complete absence of congestive signs, all point to the benignity of systolic gallop rhythm.

It appears that none of the proposed theories as to causation of the extra sound can satisfactorily account for all cases.

AUTHOR.

Nelson, H. B., and Eades, M. F.: Some Obstetrical Aspects of Cardiac Disease Complicated by Pregnancy. New England J. Med. 213: 1057, 1935.

A series of 495 patients with rheumatic heart disease complicated by pregnancy has been analyzed.

Ninety-two per cent of the cardiac failures occurred during pregnancy. Forty-seven per cent of the failures occurred in the seventh and eighth months of pregnancy. If a pregnant cardiac patient is able to go through the eighth month of pregnancy without failure, her chance of decompensation with proper care during the ninth month or during delivery should be relatively small. The authors were unable to demonstrate in this series of cases that the cardiac patient has any shorter or easier labor than the normal woman.

Sixty-seven and three-tenths per cent of these patients were delivered by the pelvic route and 32.7 per cent by abdominal route. The majority of patients in actual decompensation had abdominal deliveries. In spite of our attempts to obviate the second stage of labor, 63.4 per cent of the multiparas and 14.1 per cent of the primiparas were delivered normally, an incidence of 49.8 per cent of normal deliveries for the entire group. The low incidence of difficult pelvic deliveries is to be noted; also the increased incidence of easy artificial termination in an effort to obviate the second stage of labor. Sterilization was performed in 23.6 per cent of the cardiac cases.

In the 495 cases here studied, the mortality rate was 4.6 per cent. The incidence of mortality was little higher in patients delivered in failure than in those without. The importance of treating the pregnant cardiac patient primarily as a medical problem and secondarily as an obstetrical problem is emphasized.

AUTHOR.

Gant, J. C.: Myxedema Heart: Report of a Case. New England J. Med. 213: 918, 1935.

This report adds to the literature one more case of congestive heart failure associated with myxedema. That congestive failure was present is shown by the dyspnea and peripheral edema with the pulmonary congestion shown both by auscultation and x-ray. Part of the gross enlargement here shown is no doubt due to the dilatation usually accompanying congestive failure. In this case the picture may not be due to uncomplicated myxedema, in view of the persistent intraventricular block and rather rapid heart on only 1.5 gr. of thyroid substance. However, the fact that the patient is now active without any signs of failure suggests that myxedema is the added factor responsible for the heart failure.

Myxedema as one of the causes for auricular fibrillation is suggested by this case. This seems strange in view of the frequency of this arrhythmia in hyperthyroidism. That normal rhythm was established coincidentally with the giving of thyroid in this case is a fact worth noting. The possibility of its being a coincidental finding is recognized.

AUTHOR.

Abt, Arthur F.: Erythema Annulare Rheumaticum. Am. J. M. Sc. 190: 824, 1935.

Erythema annulare rheumaticum is exclusively associated with rheumatic endocarditis, and its appearance has been noted only in association with such cases. The occurrence of this rash in children suffering with rheumatic endocarditis, as is

the case with other cutaneous lesions found in this disease, may be considered as evidence of either the persistence of an active rheumatic endocarditis or as a sign of reactivation of the disease.

AUTHOR.

Starr, S., and Parrish, P.: Rheumatic Pleurisy, With Particular Reference to Its Demonstration by Roentgen Study. Am. J. Dis. Child. **50**: 1187, 1935.

Routine anteroposterior and oblique views of the chest frequently demonstrate rheumatic interlobar pleurisy during the active phases of rheumatic fever.

By roentgen ray studies of an unselected series of hospitalized children, interlobar pleural thickening was demonstrated in 9 per cent of "normal" children, in 13.5 per cent of children with chorea alone, and in 43.6 per cent of children with other manifestations of rheumatic fever.

The incidence of thickened pleura in the group with rheumatic infection bears no relation to the incidence of previous pneumonia, pulmonary congestion of cardiac decompensation, or tuberculosis of childhood.

The greatest percentage of pleurisy was found to be associated with rheumatic pericarditis clinically, at autopsy, and by roentgen ray examination.

AUTHOR.

Rodrigue, Carlos, and Battro, Antonio: Aorta and Rheumatism. Rev. argent. de cardiol. **2**: 170, 1935.

A survey of the literature suggests that there is no absolute proof of the existence of aneurysms of rheumatic origin since no anatomical-pathological control has ever been carried out. Rheumatic inflammatory reactions of the aorta have been satisfactorily demonstrated, but they are never so extensive as to cause destruction of the elastic layer.

The two observations reported here are of simultaneous aortic stenosis and regurgitation of rheumatic origin which showed obvious radiological alterations of the vascular shadow. Necropsy, on the other hand, revealed practically normal aortas in both cases. The cause of the roentgenological alterations must be interpreted as functional in character. Under these circumstances the radiological diagnosis of aneurysm and rheumatic aortitis are misinterpretations of the vascular shadow.

The authors are inclined to believe that rheumatic aortic lesions are of no great clinical importance. Aneurysms and aortitis therefore should continue to be regarded as synonymous with syphilis.

AUTHOR.

Banerjea, J. C.: Rheumatic Heart Disease in Childhood. Indian J. Pediat. **2**: 279, 1935.

The following is a summary of the observations based on an analytical study of 25 cases of rheumatic heart disease in childhood found among 85 cases of cardiac rheumatism in a series of 256 consecutive cardiac cases seen in hospital and private practice.

Rheumatic infection was found to play an important rôle in the causation of heart disease in India. About one-third (33.2 per cent) of all cases of organic heart disease in this series had a rheumatic etiology.

Twenty-two out of 25 patients (88 per cent) were found to belong to the poorer classes.

The curve of age incidence for rheumatic heart disease began at four to six years, rose to its peak at ten to twelve years, and then declined at thirteen to fifteen years. There was a marked preponderance of males over females. A familial incidence was observed in 24 per cent of the cases.

Close inquiry revealed a history of one or more attacks of swollen or painful joints of a mild or severe type with or without fever occurring some time or other in course of the evolution of rheumatic heart disease in 19 out of 25 cases (76 per cent). A history of tonsillitis or sore throat was present in 32 per cent of cases.

Chorea was not seen in any of the cases presented here.

Subcutaneous nodules are probably not so rare as one is likely to believe. They were present in 2 cases out of 25 (8 per cent).

Active rheumatic carditis was present in 3 cases, mitral stenosis in 15 (60 per cent), aortic incompetence in 2 (8 per cent), and mitral stenosis combined with aortic incompetence in 3 (12 per cent). In one case a tentative diagnosis of aortic stenosis was made in addition to aortic incompetence and mitral stenosis.

Most of the cases (52 per cent) came under observation with moderate or marked cardiac enlargement associated with symptoms and signs of congestive failure.

Relapses were found to occur in 40 per cent of cases as compared with 70 per cent in the West.

In treatment absolute rest in bed was considered to be most essential. Salicylates in large doses with double the dose of sodium bicarbonate were found to be successful in relieving joint pains and in reducing the course of the febrile attack. Digitalis with ammonium chloride was found to be of great value in cases of congestive failure. The sedimentation rate of the erythrocytes was considered to be very helpful in deciding how long a patient with a rheumatic heart should be kept under strict bed rest.

The mortality of the cases in this series was 4 per cent in two years and 24 per cent in ten years from the onset of the illness.

AUTHOR.

Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. IV. Characteristics of Strains of Hemolytic Streptococcus, Effective and Non-Effective, in Initiating Rheumatic Activity. J. Clin. Investigation **14**: 755, 1935.

The biological characteristics of strains of hemolytic streptococcus associated with acute pharyngitis in rheumatic subjects have been studied.

Half of the strains selected initiated intense activity of the rheumatic process and the other half failed to initiate rheumatic activity in susceptible subjects.

The cultural characteristics of the organisms studied were essentially the same in both groups. All strains were of human type.

The effective organisms were characterized by the capacity to produce strong skin toxins and streptolysins and were indistinguishable from scarlatinal strains of *Streptococcus hemolyticus*. They gave rise to the development of high titers of antistreptolysin in the subjects infected.

Those strains which failed to produce skin toxin and streptolysin, and did not give rise to the development of high titers of antistreptolysin, were ineffective in activating the rheumatic process.

AUTHOR.

Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. V. Active and Passive Immunization to Hemolytic Streptococcus in Relation to the Rheumatic Process. J. Clin. Investigation **14**: 763, 1935.

Active immunization with streptococcus toxin neither prevents streptococcus infection nor inhibits the development of the rheumatic process.

The introduction of protective antibodies just prior to the expected attack does not decrease and may possibly increase the intensity of the rheumatic recrudescence.

The development of rheumatic activity appears to depend not only upon infection with a toxin-producing strain of hemolytic streptococcus, but also upon the host's immune response to this infection. AUTHOR.

Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. VI. The Significance of the Rise of Antistreptolysin Level in the Development of Rheumatic Activity. J. Clin. Investigation **14**: 769, 1935.

The median of the antistreptolysin determinations on 176 individuals in good health was 71 units. This is somewhat higher than the natural human level of 50 units.

The median titer developed in acute rheumatism was 500 units, and the geometric mean 490 units. In most instances the titer returned to approximately natural level within a period of one year.

The onset of acute rheumatism coincided with a sharp rise in antistreptolysin titer.

Rheumatic patients infected with hemolytic streptococcus who escaped recrudescence showed little or no change in antistreptolysin titer.

The relation of the immune response of the host to the development of rheumatic activity is discussed. AUTHOR.

Coburn, A. F., and Pauli, Ruth H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. VII. Splenectomy in Relation to the Development of Rheumatic Activity. J. Clin. Investigation **14**: 783, 1935.

Splenectomy did not permanently modify either the immune response or the character of the rheumatic recrudescence.

Nine out of twenty apparently quiescent rheumatic subjects developed recrudescences as a direct sequel to splenectomy.

All of these nine individuals had elevated antistreptolysin titers at the time of operation, and none of them showed any increase in titer during or after the recrudescence.

This shows that following operative manipulation of antibody-producing tissue during subsiding rheumatism, an exacerbation of symptoms may develop in the absence of further rise in antistreptolysin titer. AUTHOR.

Moore, A. G.: Incidence of Cardiac Diseases. J. Indiana M. A. **28**: 419, 1935.

It was found that 77.7 per cent of the cardiovascular abnormalities were in the hypertensive group. The author believes the increased nervous tension of today is responsible for the constantly increasing cases in this group. The study shows that individuals with hypertension have a little longer span of life than those in the valvular or nonhypertensive group.

Primary occurrences of cases in the valvular group, especially in the earlier age findings, are probably due to intercurrent infections. Palpable arteriosclerosis becomes established five years earlier in the hypertensive group than in the nonhypertensive group, but following this, it is increased in practically the same ratio for both groups.

Lewis, Thomas: The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot Poisoning. Clin. Sc. **2**: 43, 1935.

The poison ergotoxine constricts the arteries of the comb; this constriction is one that cannot be released by relaxation of vasomotor tone or by local warming. The constriction is maintained if ergot injections are repeated day by day, but it is insufficient to stop the blood flow through the comb, which continues a little

warmer than the surrounding atmosphere and shows at first no signs of desiccation. About the third or fourth day the nutrition of the walls of the vessels begins to suffer, for about this time stasis occurs in them, the blood in the capillaries being in a state rendering its dislodgment difficult.

Ergot produces its ultimate effects entirely through arterial spasm; a direct poisoning of the tissues seems to play no part. The vasoconstriction does not lead directly to tissue necrosis but to damage to the walls of the vessels resulting in dilatation, and in stasis or thrombosis, either of which will bring the circulation locally to an end and together determine dry necrosis.

E. A.

Katz, L. N., Lindner, E., and Landt, H.: On the Nature of the Substance (S) Producing Pain in Contracting Skeletal Muscle: Its Bearing on the Problems of Angina Pectoris and Intermittent Claudication. J. Clin. Investigation 14: 807, 1935.

The main findings in this study with regard to the amount of exercise required to cause pain and fatigue in the muscles of the arms of normal subjects are:

a. Circulatory slowing caused a decrease in the amount of exercise required to cause pain, the effect being disproportionately greater at high degrees of circulatory slowing. The amount of blood trapped in the arm played an insignificant rôle. Circulatory slowing had its greatest effect at the fastest rates of exercise.

b. Increasing the rate of exercise led to a decrease in the amount of exercise required to cause pain when the circulation to the limb was unobstructed. Slowing the circulation led to a diminution of this effect of rate of exercise. This effect of rate of exercise disappeared when the circulation in the limb was stopped.

c. Exercise of a large group of muscles of the leg to the point of pain had a twofold action on the amount of exercise required to cause pain in a subsequent arm exercise; viz., (1) by an action on the central nervous system it augmented the amount of exercise required to cause pain, and (2) by an action through transport of blood from the exercised legs to the muscles of the arm it decreased the amount of exercise required to cause pain. Special procedures were required to separate these two effects.

d. Increasing the CO_2 content of the blood in the arm decreased the amount of exercise required to cause pain. Ingestion of large amounts of sodium bicarbonate increased the amount of exercise required to cause pain. Ingestion of sodium bicarbonate also tended to alleviate the pain of patients with intermittent claudication and those with angina pectoris.

e. In right-handed subjects less exercise was required to cause pain in the left than in the right arm.

f. The effects of these procedures on neuromuscular fatigue were not related quantitatively to their effects on pain. With certain procedures, such as the ingestion of sodium bicarbonate, the effects were opposite.

The significance of these results on pain and fatigue in muscle is discussed in the body of the paper. The salient conclusions from these experiments are:

a. The time allowed for recovery between contractions in a rhythmically contracting muscle alters the rate of accumulation of the substance (s) leading to pain, implying that the pain-producing substance (s) is a product of metabolic muscular activity.

b. The substance (s) causing pain diffuses into and out of the blood stream. It is nonvolatile since it operates even after passing through the lungs.

c. The appearance of pain in muscle is dependent not only upon the local production of pain-producing substance (s) but to a certain extent upon the transport of such a substance (s) from other regions.

d. This nonvolatile pain-producing substance (s) appears to be acid in character; at least its action is facilitated by acid and retarded by alkaline substances.

e. Acids and bases exhibit summation of effect with the pain-producing substance (s) by changing the pH of the end-organs, by altering the buffering capacity of the muscle concerned.

f. Training tends to lessen the action of the pain-producing substance (s) probably by altering the buffering capacity of the muscle concerned.

g. The variability in the appearance of fatigue, which is independent of pain, plays an important rôle in forestalling the appearance of pain under certain circumstances.

The bearing of these findings on the appearance of pain in angina pectoris and in intermittent claudication is discussed at the end of each section.

AUTHOR.

Grant, R. T.: A Portable Thermo-electric Couple for Measuring Skin Temperature. Guy's Hosp. Rep. **85:** 209, 1935.

The apparatus described by Grant is a modification of that developed by Sir Thomas Lewis, in which the circuit has been simplified. A sensitive, but robust, pointer galvanometer is used instead of the mirror instrument, and temperatures are read directly from the galvanometer scale. It has proved serviceable in studying disturbances of the peripheral circulation at the bedside.

L. H. H.

Harris, R. I.: The Rôle of Sympathectomy in the Treatment of Peripheral Vascular Disease. Brit. J. Surg. **23:** 414, 1935.

Significant improvement in symptoms and course of Buerger's disease was obtained in 79 per cent of 24 cases subjected to lumbar sympathetcomy (21 cases) and stellate ganglionectomy (3 cases).

In this disease Harris believes that a good result of operation can be predicted if one obtains a preoperative definite rise of skin temperature under spinal anesthesia or nerve block.

In peripheral arteriosclerosis the number of cases in which vasospasm is a factor warranting the risk of this operation is small. In five of twelve such cases, appreciable benefit was obtained, which has lasted sufficiently long to justify the operation. Four cases of Raynaud's disease so treated were improved.

An operative technic is given.

L. H. H.

Baena, V.: Determination of the Circulating Blood Volume With a Spectrophotometric Method. Ztschr. f. d. ges. exper. Med. **96:** 420, 1935.

A modification of Haldane's carbon-monoxide method, using Bechstein's spectrophotometer instead of a calorimeter, was used. The spectrophotometer appears more reliable and accurate than the calorimeter in determining the amount of carbon-monoxide hemoglobin and circulating blood volume.

In experimenting with rabbits, the volume of circulating blood determined by this method was found to be one-fourteenth of the body weight. Injection of thyroxin increased the volume of circulating blood, whereas ice bags applied to the body to activate the thermo-regulating mechanism produced no change.

J. K.

Irving, Lawrence, and Welch, Mary Scott: The Effect of the Composition of the Inspired Air on the Circulation Through the Brain. Quart. J. Exper. Physiol. **25:** 121, 1935.

The flow of blood through the femoral vein and longitudinal sinus of the dog was examined by comparison of the A-V oxygen differences. Inhalation of 10

per cent carbon dioxide in oxygen increased blood flow through the brain of anesthetized dogs to the estimated extent of from two to four times. At the same time flow through the hind leg was diminished often to less than half the normal rate. These vascular changes indicate a differential vascular control giving preferential consideration to the brain. The stimulus for differential control may originate in the brain itself, but the result may be reinforced by, or it may even originate in, a site extrinsic to the tissue.

E. A.

Allen, Edgar V., and Ghormley, R. K.: Lymphedema of the Extremities: Etiology, Classification and Treatment; Report of 300 Cases. Ann. Int. Med. **9**: 516, 1935.

Three hundred cases of lymphedema are classified clinically in two main groups depending upon the presence or absence of clinical evidence of infection. Noninflammatory lymphedema is of the primary or secondary type; under the former classification are considered lymphedema praecox and congenital lymphedema and under the latter classification are considered lymphedemas due to occlusion of lymph nodes. Inflammatory lymphedema is considered under the heading of primary and secondary inflammatory lymphedema depending upon whether the inflammation arises spontaneously or whether it is secondary to venous stasis, trichophytosis, and so forth. The various clinical types of lymphedema present widely diverse clinical manifestations, but the symptoms and development of each type are characteristic within rather narrow boundaries. The clinical classification is not supported by pathological studies as only congenital lymphedema is characteristic pathologically.

Lymphedema in man results from multiple causes, but the mechanism of its productions appears to be the same in all cases. Lymph stasis occurs as a result of lymphatic obstruction; the intralymphatic pressure increases and causes dilatation of lymph vessels with consequent insufficiency of valves and further lymph stasis. The protein content of lymph increases and fibroblasts proliferate rapidly and cause fibrosis. As a result of an increased quantity of lymph in the tissues, inflammation may occur producing lymphatic thrombosis and further stasis. The cycle, which is a vicious one, consists of lymph stasis, fibrosis, inflammation with further stasis and more fibrosis. Medical treatment consists in prevention of lymph stasis by adequate bandaging of the limbs. If this is done, there will be no progressive enlargement of the limb due to fibrosis. Surgical treatment is an attempt to correct the consequences of inadequate medical supervision. The Kondoleon operation is the most satisfactory; it is viewed solely as a plastic procedure whereby hypertrophied skin and subcutaneous tissues are removed. The results, while fairly good, are not entirely satisfactory.

AUTHOR.

Dandy, Walter E.: The Treatment of Carotid Cavernous Arteriovenous Aneurysms. Ann. Surg. **102**: 916, 1935.

Arteriovenous aneurysms of the type indicated are more common than arteriovenous fistulas in any other part of the body. About three-fourths of the fistulas are traumatic; the others occur spontaneously as a result of congenital or acquired aneurysms. The clinical syndrome consists of exophthalmos, pulsation of the protruding eye, and a subjective roar which to auscultation is a systolic murmur. Cure is not dependent upon isolation of the aneurysm by occlusion of the carotid, but by thrombosis in the fistula, the carotid artery or venous tributaries. In each of two instances in which arterial ligations had not cured the fistulas, a silver clip was placed upon the intracranial portion of the internal carotid artery. In one case

there was immediate and complete cure; in the other case it was necessary to excise most of the collateral branches entering the ophthalmic artery to complete the cure.

E. A.

Scupham, G. W., and de Takáts, G.: Peripheral Vascular Diseases. A Review of Some of the Recent Literature With a Critical Review of Surgical Treatment. Arch. Int. Med. **56**: 530, 1935.

The review is in two parts; the first, an excellent presentation of the salient features of the many recent advances in the general field of the peripheral circulation, the second, a surgeon's critical summary of most of the surgical aspects of treatment.

By far the greater part of the work reviewed has been done in the past five years; its extent is indicated by the use of 90 pages of the journal for an exceedingly meaty consideration of some 260 articles.

In the field of the physiology of the peripheral circulation Sir Thomas Lewis is being followed by several able investigators. Most important advances have been made in the field of conservative therapy based on new physiological discoveries. Furthermore, as the various disorders are better understood and are diagnosed earlier, much of the previous therapy is being discarded. The operation of periarterial sympathectomy, for instance, is being limited much more strictly than in the early days of enthusiasm. The etiology of Buerger's disease remains unsolved, but its early recognition and treatment are aided by recent investigation.

L. H. H.

Liu, A. C., and Rosenblueth, A.: Reflex Liberation of Circulating Sympathin. Am. J. Physiol. **113**: 555, 1935.

Direct stimulation of sympathetic nerves leads to the passage into the blood of sympathin, a sympathomimetic substance the presence of which may be demonstrated by reactions of adequate denervated autonomic effectors. The question arises, Can reflex activation of sympathetic nerves cause sympathin to pass into the blood? Controlled experiments on cats show that stimulation of the sciatic or one of the brachial nerves causes contraction of the nictating membrane, a manifestation of circulating sympathin under conditions of the experiment. While sympathin originates from sympathetic nerves, its presence in the blood in the experiments did not depend upon certain parts of the sympathetic nervous system, as contractions of the nictating membrane occurred when the thoracic sympathetics were present and the cephalic and abdominal sympathetics were absent, as well as when conditions were reverse. It appears that sympathin may play a rôle as a hormone in certain physiological conditions.

E. A.

Ash, Rachel: Use of Typhoid Vaccine in Treatment of Chorea: Its Possible Dangers, Am. J. Dis. Child. **50**: 879, 1935.

Intravenous injections of typhoid vaccine may be of harm in the presence of carditis.

During the febrile reaction following intravenous injections of typhoid vaccine, there is a depression of granulocytes. This method of therapy should be checked by frequent determinations of the white blood cell count.

Typhoid vaccine therapy does not prevent a recurrence of chorea.

Book Review

ELEKTROKARDIOGRAPHISCHE BEFUNDE BEI HERZINFARKT. By Doctor Anton Jervell. Acta Medica Scandinavica, Supplementum LXVIII, Kristes Boktrykkeri, Oslo, 1935.

This monograph, in German, is devoted to the description and classification of the electrocardiographic findings in sixty-five cases of myocardial infarction. The cases were not selected; all the cases observed during the period of the study in which a clinical diagnosis of myocardial infarction was made are included. In addition to the standard leads, a precordial lead from the region of the apex was taken in more than one-half the cases (thirty-six). In taking this lead the galvanometer connections were so arranged that negativity of the exploring electrode was represented by a downward, instead of by an upward, deflection, and the indifferent electrode was placed on the back. Serial electrocardiograms were taken in the great majority of the cases, and twenty-six of the patients studied came to autopsy. The case histories are given in an appendix. The illustrations include reproductions of the initial and some of the subsequent electrocardiograms in each case, and also sketches showing the location of the infarct when this was determined by autopsy.

Extrasystoles were observed in thirty-four cases, auricular flutter or fibrillation in seven, auricular paroxysmal tachycardia in one, atrioventricular heart-block in three, prolonged conduction time in three, sino-auricular block in one, and dissociation with interference in one. The ventricular complex was abnormal in all cases. Bundle-branch block of the common type was present in seven cases, bundle-branch block of the uncommon type in one, arborization block in five, small complexes without intraventricular block in fourteen, large Q-waves in Lead III in nineteen, and large Q-waves in Lead I in five.

Displacement of the RS-T segment (1 to 8 mm.) was observed in most instances in which the patient came under observation shortly after the coronary accident, but was not always maximal in the first curve taken. It persisted longer in the precordial lead than in the standard leads. Progressive T-wave changes occurred both in those cases which showed RS-T displacement and in those which did not. The T-wave changes reached their height in from two weeks to three months after the beginning of infarction. In thirty-five cases the T-wave changes were of the T_1 type; in twenty-six cases they were of the T_2 type. Changes in the RS-T segment and in T were the most valuable as an aid in diagnosis; they occurred in forty-nine of the sixty-five cases. The precordial lead was found invaluable and showed characteristic changes in twenty-six of the thirty-six cases in which it was used. It showed such changes in all but one of the twenty-one cases in which the standard curves were of the T_1 type and in five of the twelve cases in which the standard curves were of the T_2 type.

Arborization block appeared to be of serious prognostic import, but the other electrocardiographic abnormalities did not seem to be of any help in foretelling the outcome. In sixteen of the twenty-six cases which came to autopsy, the infarct involved the anterior wall of the heart; in the remaining ten it involved the posterior wall. In eleven of the cases in which the infarct was anterior, the standard leads were of the T_1 type; in three cases arborization block was present, and in the remaining two cases the standard leads could not be classified as be-

longing either to the T_1 or to the T_3 class. In all of the ten cases in which the infarct was posterior, the standard leads showed changes of the T_3 type. It is suggested that changes of the T_1 type are sometimes absent when the infarct is anterior because anterior infarcts frequently extend to the apical portions of the posterior wall.

The author was able in the case of very thin normal subjects to produce inversion of the T deflection in the precordial lead employed by placing an ice bag over the heart for a half hour or longer.

This monograph is a very valuable contribution to our knowledge of the electrocardiographic changes produced by myocardial infarction. It is particularly valuable because it deals with a comparatively large series of unselected cases and because of the large number of autopsies obtained. It is very well written and profusely illustrated. The list of references includes all of the more important and many of the less important papers dealing with the electrocardiogram in myocardial infarction which have appeared either in America or in Europe.

F. N. W.